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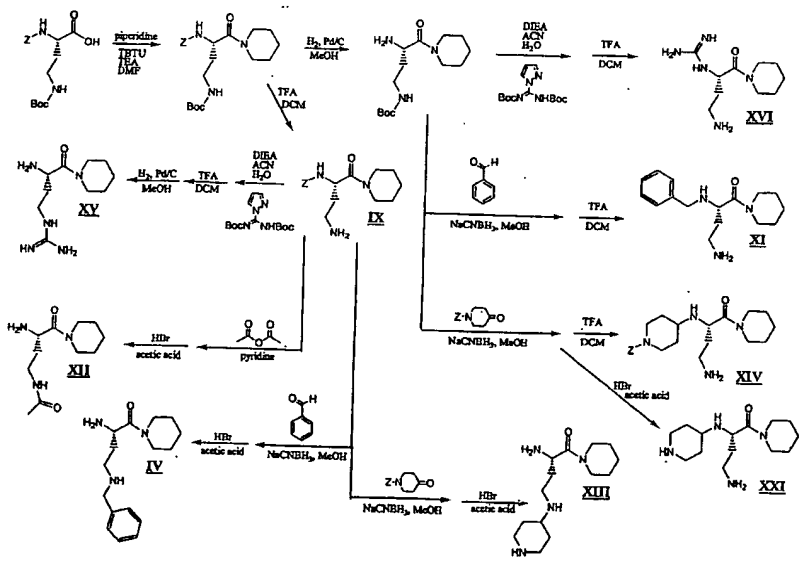
(54) Title: DIPEPTIDYL PEPTIDASE INHIBITORS



(57) Abstract: The present invention relates to novel inhibitors of serine type peptidases in general and of serine type dipeptidyl peptidases in particular. The present invention further relates to the use of the dipeptidyl peptidase inhibitors for selective inhibition of dipeptidyl peptidases. The present invention also relates to pharmaceutical compositions comprising these novel dipeptidyl peptidase inhibitors. The present invention further relates to the use of the novel inhibitors in therapy, diagnosis and research.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Dipeptidyl peptidase inhibitors

Field of the invention

The present invention relates to novel inhibitors of serine type peptidases in general and of serine type dipeptidyl peptidases in particular. The present invention further relates to the use of the dipeptidyl peptidase inhibitors for selective inhibition of serine type peptidases. The present invention also relates to pharmaceutical compositions comprising these novel dipeptidyl peptidase inhibitors. The present invention further relates to the use of the novel inhibitors in therapy, diagnosis and research.

Background of the invention

Serine type proteases serve an important role in human physiology by mediating the activation of vital functions. In addition to their normal physiological function, serine proteases have been implicated in a number of pathological conditions in humans. Serine proteases are characterized by a catalytic triad consisting of aspartic acid, histidine and serine at the active site.

Serine peptidases like granzymes, mast cell tryptase, elastases, trypsin-like enzymes, prolyl oligopeptidase, and serine type dipeptidyl peptidases such as DPPII, DPPIV, QPP, FAPα, DPP8 and DPP9 are involved in various processes that take place in the body, such as blood coagulation, inflammation, immune response, and control of peptide hormone metabolism in general.

Dipeptidyl peptidases (DPPs, EC 3.4.14) have been identified in various mammalian tissues and catalyze the sequential release of dipeptides from peptides. Among these enzymes, DPP II (EC 3.4.14.2) and DPP IV (EC 3.4.14.5) preferentially release N-terminal dipeptide moieties (Xaa-Pro- or Xaa-Ala-) from some oligopeptides or proteins. Although DPP IV and DPP II share substrate specificity, they can be functionally and biochemically distinguished.

Dipeptidyl peptidase IV is a highly specific exopeptidase with a serine type mechanism of peptidase activity, cleaving off dipeptides from the amino-terminus of peptides with proline or alanine at the penultimate position. In addition the slow release of dipeptides of the type X-Gly or X-Ser is reported for some naturally occurring peptides. DPP IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues, and is also found

in body fluids. In the hematopoietic system, DPP IV was identified as the leukocyte antigen CD26.

DPP II, first identified by McDonald at al. (S. *J. Biol. Chem., 1968, 243, 4143-4150*), is believed to be involved in the physiological breakdown of some proline-containing oligopeptides and neuropeptides and in the degradation of collagen (*Andersen et al. Renal Physiol. Biochem., 1989, 12, 32-40*) together with tripeptidyl peptidase and in lysosomal degradation and protein turnover. DPP II is generally localized in lysosomes and is found in a number of mammalian tissues and body fluids.. The order of expression of DPP-II is kidney > > testis > or = heart > brain > or = lung > spleen > skeletal muscle > or = liver (*Araki H et al., J Biochem (Tokyo) 2001, 129:27988*).

Dipeptidyl peptidase II and quiescent cell proline dipeptidase QPP have recently been suggested to be identical proteases based on sequence comparison of human quiescent cell proline peptidase and rat DPPII. Additional biochemical evidence is provided by Leitung (Biochem. J. on line, 2002, 1643).

It is a general object of the present invention to provide novel serine type peptidase inhibitors in general and dipeptidyl peptidase inhibitors in particular, with recognized utility and exhibiting relatively high activity at relatively low concentrations, which can be exploited in medical applications. The invention also aims to provide novel inhibitors that have a more specific and selective DPP inhibitory activity than currently available inhibitors. These and other objects and advantages of the present invention will be recognized by those skilled in the art from the following description and illustrative examples.

Summary

According to a first aspect, the invention provides compounds according to claim 1, which are able to inhibit the enzymatic activity of serine type dipeptidyl peptidases such as DPPII, DPPIV, DPP8, DPP9, FABα and QPP. Such compounds according to the present invention induce strong inhibition of dipeptidyl peptidase enzyme activity. The present novel dipeptidyl peptidase inhibitors are therefore very suitable for use in all kinds of research, therapeutic and diagnostic applications as described below.

The present invention further relates in another aspect to the use of said compounds as a medicament. In addition, the invention concerns the use of said compounds in the treatment of diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase, or in diagnostic and research methods. The present invention further relates to the use of the compounds in the preparation of a medicament for inhibiting the activity of a serine type dipeptidyl peptidase and in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase. The present invention also relates to the use of the compounds in diagnostic and research methods.

In addition, the present invention also relates to pharmaceutical compositions and kits comprising the compounds according to the invention.

In a further aspect, the present invention relates to methods for inhibiting the activity of a serine type dipeptidyl peptidase *in vitro, ex vivo* and *in vivo*.

The present invention also relates to method for purifying and synthesizing the present compounds.

Detailed description of the figures

Figure 1 illustrates the synthesis of compounds having formulas IV, IX, XI, XII, XIII, XIV, XV, XVI and XXI as illustrated in example 2, Table B.

Figure 2 illustrates the synthesis of compounds having formulas XVIII, XVII, XX as illustrated in example 2, Table B.

Figure 3 illustrates the synthesis of compounds having formulas V, VI, VII, VIII, X, XIX as illustrated in example 2, Table B.

Figure 4 illustrates the synthesis of compounds having formulas XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, XXXIV as illustrated in example 2, Table B.

Figure 5 illustrates the synthesis of compounds having formulas XXXV and XXXVI as illustrated in example 2, Table B.

Figure 6 illustrates the synthesis of compounds having formulas XXXVII to XXXXI as illustrated in example 2, Table B.

Figure 7 illustrates the synthesis of compounds having formulas XXXXII to XXXXVII as illustrated in example 2, Table B.

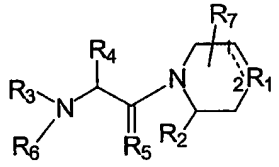
Detailed description of the invention

The present invention relates to novel inhibitors of serine type dipeptidyl peptidases such as DPPII, DPPIV, DPP8, DPP9, FABα and QPP.

As used herein the terms "serine type dipeptidyl peptidase" or "dipeptidyl peptidases" or "DPP" are used as synonyms and refer to serine type dipeptidyl peptidases such as DPPII, DPPIV, DPP8, DPP9, FABα and QPP.

In this application the terms "modulator", "inhibitor", "compound" and "modulating compound" are used interchangeably. These terms as used herein refer to compounds according to the invention having an modulating activity on DPP, which may mostly comprise inhibiting properties in various degrees going from very inhibiting to weakly inhibiting. Although the compounds will mostly have inhibiting properties, it is also within the scope of the invention that the present compounds may have in some situations enhancing properties.

In a first embodiment, the present invention relates a compound having a modulating activity on a serine type dipeptidyl peptidase, having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,



formula I

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia and imino, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3, R^4 and R^6 are selected from the group comprising hydrogen, oxyalkyl, alkyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkylamino, aminoalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, aminoalkanoyl, aminocarbonyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl,

cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^{1}oxy, Het^{1}alkyl, Het^{1}oxyalkyl, Het^{1}cycloalkyl, Het^{1}alkoxycarbonyl, Het^{1}oxycarbonyl, Het^{1}alkanoyl, Het^{1}alkyloxyalkyl, Het^{1}oxyalkylcarbonyl, Het^{1}alkyloxyalkylcarbonyl, Het^{1}aminocarbonyl, Het^{1}carbonyloxyalkyl, Het^{1}alkylcarbonyloxyalkyl, Het^{1}aryl, Het^{1}arylaminoalkoxy, Het^{1}arylamino, Het^{1}arylaminoalkyl, Het^{1}arylaminoalkylamino, Het^{1}aryloxy, Het^{1}aryloxyalkoxy, Het^{1}aryloxyalkyl, Het^{1}aryloxyalkylamino, Het^{1}aralkyl, Het^{1}aralkoxy, Het^{1}aralkylamino, Het^{1}aralkanoyl, Het^{1}aroyl, Het^{1}arylcarbonyl, Het^{1}aryloxycarbonyl, Het^{1}arylthiocarbonyl, Het^{1}aralkoxycarbonyl, Het^{1}arylalkylthiocarbonyl, Het^{1}aryloxyalkyl, Het^{1}arylthioalkyl, Het^{1}haloalkyl, Het^{1}aryloxycarbonylalkyl, Het^{1}aryloxyalkanoyl, Het^{1}aralkylcarbonyloxyalkyl, Het^{1}arylaminocarbonyl, Het^{1}aralkylaminocarbonyl, Het^{1}alkylaminoalkyl, Het^{1}aralkylaminoalkyl, Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl,

Het^1aralkanoylaminoaryl, Het^1alkyloxycarbonylaminoaryl, Het^1aryloxycarbonylaminoaryl, Het^1aralkoxycarbonylaminoaryl, Het^1alkylaminocarbonylaminoaryl, Het^1arylaminocarbonylaminoaryl, Het^1aralkylaminocarbonylaminoaryl, Het^1alkylaminoaralkyl, Het^1arylaminoaralkyl, Het^1aralkylaminoaralkyl, Het^1alkanoylaminoaralkyl, Het^1aroylaminoaralkyl, Het^1aralkanoylaminoaralkyl, Het^1alkyloxycarbonylaminoaralkyl, Het^1aryloxycarbonylaminoaralkyl, Het^1aralkoxycarbonylaminoaralkyl, Het^1alkylaminocarbonylaminoaralkyl, Het^1arylaminocarbonylaminoaralkyl, Het^1aralkylaminocarbonylaminoaralkyl, Het^2, Het^2oxy, Het^2alkyl, Het^2oxyalkyl, Het^2cycloalkyl, Het^2alkoxycarbonyl, Het^2oxycarbonyl, Het^2alkanoyl, Het^2alkyloxyalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aminocarbonyl, Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aryl, Het^2arylaminoalkoxy, Het^2arylamino, Het^2arylaminoalkyl, Het^2arylaminoalkylamino, Het^2aryloxy, Het^2aryloxyalkoxy, Het^2aryloxyalkyl, Het^2aryloxyalkylamino, Het^2aralkyl, Het^2aralkoxy, Het^2aralkylamino, Het^2aralkanoyl, Het^2aroyl, Het^2arylcarbonyl, Het^2aryloxycarbonyl, Het^2arylthiocarbonyl, Het^2aralkoxycarbonyl, Het^2arylalkylthiocarbonyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2haloalkyl, Het^2aryloxycarbonylalkyl, Het^2aryloxyalkanoyl, Het^2aralkylcarbonyloxyalkyl, Het^2arylaminocarbonyl, Het^2aralkylaminocarbonyl, Het^2alkylaminoalkyl, Het^2aralkylaminoalkyl, Het^2alkanoylaminoalkyl, Het^2aroylaminoalkyl, Het^2aralkanoylaminoalkyl, Het^2alkyloxycarbonylaminoalkyl, Het^2aryloxycarbonylaminoalkyl, Het^2aralkoxycarbonylaminoalkyl, Het^2alkylaminocarbonylaminoalkyl, Het^2arylaminocarbonylaminoalkyl, Het^2aralkylaminocarbonylaminoalkyl, Het^2alkylaminoaryl, Het^2arylaminoaryl, Het^2aralkylaminoaryl, Het^2alkanoylaminoaryl, Het^2aroylaminoaryl, Het^2aralkanoylaminoaryl, Het^2alkyloxycarbonylaminoaryl, Het^2aryloxycarbonylaminoaryl, Het^2aralkoxycarbonylaminoaryl, Het^2alkylaminocarbonylaminoaryl, Het^2arylaminocarbonylaminoaryl, Het^2aralkylaminocarbonylaminoaryl, Het^2alkylaminoaralkyl, Het^2arylaminoaralkyl, Het^2aralkylaminoaralkyl, Het^2alkanoylaminoaralkyl, Het^2aroylaminoaralkyl, Het^2aralkanoylaminoaralkyl, Het^2alkyloxycarbonylaminoaralkyl, Het^2aryloxycarbonylaminoaralkyl, Het^2aralkoxycarbonylaminoaralkyl, Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

wherein R^3, R^4 and R^6 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl,

arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, and

wherein R^7 is selected from the group comprising hydrogen, alkyl and halogen.

According to the present invention, it was then found that all of the compounds of formula I claimed in claim 1 and their corresponding pharmaceutically acceptable salts are useful in inhibiting serine type dipeptidyl peptidases and are potent modulators, in particular inhibitors, of DPPII in particular. Specific members of the cited R groups will be listed below.

The highly specific and potent inhibitors of serine type dipeptidyl peptidases, according to the present invention, can advantageously be used to unravel of the physiological functions of the serine type dipeptidyl peptidase enzyme and are also very useful to differentiate between different serine type dipeptidyl peptidases activity in biological systems.

The term "alkyl", alone or in combination, means straight and branched chained saturated hydrocarbon radicals containing from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms. Examples of such radicals include but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, pentyl, iso-amyl, hexyl, 3-methylpentyl, octyl and the like.

The term "cycloalkyl" alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or polycyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 7 carbon atoms. Examples of monocyclic cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Examples of polycyclic cycloalkyl radicals include decahydronaphthyl, bicyclo [5.4.0] undecyl, adamantyl, and the like.

The term "cycloalkylalkyl" means an alkyl radical as defined herein, in which at least one hydrogen atom on the alkyl radical is replaced by a cycloalkyl radical as defined herein. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term "alkoxy" or "alkyloxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, hexanoxy and the like.

The term "alkanoyl" or "alkylcarbonyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

The term "alkylamino", alone or in combination, means an alkyl amine radical (i.e. RNH-), wherein the term "alkyl" is defined as above. Examples of alkylamino radicals include methylamino ($NHCH_3$), ethylamino ($NHCH_2CH_3$), n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-hexylamino, and the like.

The term "aminoalkyl", alone or in combination, means an amine alkyl radical (i.e. NH_2R-), wherein the term "alkyl" is defined as above.

The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aryl" alone or in combination, is meant to include phenyl and naphtyl which both may be optionally substituted with one or more substituents independently selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, Het^1, amido, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, and phenyl optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro,

cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, Het^1, optionally mono- or disubstituted aminocarbonyl, methylthio and methylsulfonyl; whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het^1, Het^1alkyl, Het^1alkyl, Het^1oxy, Het^1oxyalkyl, phenyl, phenyloxy, phenyloxyalkyl, phenylalkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl. Examples of aryl includes phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like.

As used herein, the term "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "haloalkyl" alone or in combination, means an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen, preferably, chloro or fluoro atoms, more preferably fluoro atoms. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "Het^1" alone or in combination, is defined as a saturated or partially unsaturated monocyclic, bicyclic or polycyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by alkyl, alkyloxy, halogen, hydroxy, oxo, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl and a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 12 ring members which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het^2, Het^2alkyl, Het^2oxy, Het^2oxyalkyl, aryl,

aryloxy, aryloxyalkyl, aralkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl.

The term "Het^{2}" as a group or part of a group is defined as an aromatic monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by alkyl, alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl, Het^{1} and an aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 12 ring members; whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het^{1}, Het^{1}alkyl, Het^{1}oxy, Het^{1}oxyalkyl, aryl, aryloxy, aryloxyalkyl, aralkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl.

The term "arylamino" alone or in combination means an aryl amine radical, wherein the term "aryl" is defined as above.

The term "aralkyl" alone or in combination, means an alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkyl radicals include benzyl, phenethyl, dibenzylmethyl, methylphenylmethyl, 3- (2-naphthyl)-butyl, and the like.

The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like.

The term "aralkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkoxy radicals include 2-phenylethoxy, 2-phenyl-1-propoxy, and the like.

The term "aralkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylamino radicals include 2-phenethylamino, 4-phenyl-n-butylamino, and the like.

The term "aroyl" means an acyl radical derived from an arylcarboxylic acid, aryl having the meaning given above. Examples of such arylcarboxylic acid radicals include substituted and unsubstituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamidol-2-naphthoyl, and the like.

The term "arylaminoalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkoxy radicals include 2- (phenylamino)-ethoxy, 2- (2- naphthylamino)-1-butoxy, and the like.

The term "arylaminoalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of arylaminoalkyl radicals include phenylaminoethyl, 4- (3-methoxyphenylamino)- 1-butyl, and the like.

The term "arylaminoalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkylamino radicals include 3- (naphthylamino)-propylamino, 4- (phenylamino)-1-butylamino, and the like.

The term "aryloxy" means a radical of the formula aryl-O-in which the term aryl has the significance given above.

The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above.

The term "aryloxyalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkoxy radicals include 2-phenoxyethoxy, 4- (3-aminophenoxy)-1- butoxy, and the like.

The term "aryloxyalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of aryloxyalkyl radicals include phenoxyethyl, 4- (3-aminophenoxy)-l-butyl, and the like.

The term "aryloxyalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkylamino radicals include 3-phenoxy-npropylamino, 4-phenoxybutylamino, and the like.

The term "arylthioalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkoxy radicals include 2-(phenylthio)-ethoxy, and the like.

The term "alkylthio" means an alkyl thioether radical, wherein the term "alkyl" is defined as above. Examples of alkylthio radicals include methylthio (SCH_3), ethylthio (SCH_2CH_3), n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-hexylthio, and the like.

The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl.

The term "aralkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylthio radicals include 3-phenyl-2-propylthio, 2- (2-naphthyl)-ethylthio, and the like.

The term "arylaminoalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkylthio radicals include 2- (phenylamino)- ethylthio, 3- (2-naphthylamino)-n-propylthio, and the like.

The term "aryloxyalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkylthio radicals include 3-phenoxypropylthio, 4 (2-fluorophenoxy)-butylthio, and the like.

The term "arylthioalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkylamino radicals include 2- (phenylthio)- ethylamino, and the like.

The term "arylthioalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkylthio radicals include 2- (naphthylthio)- ethylthio, 3- (phenylthio)-propylthio, and the like.

The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the meaning given above.

The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, alkanoylamino, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl.

The term "Het^2alkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkoxy radicals include 2-pyridylmethoxy, 4- (l-imidazolyl)-butoxy, and the like.

The term "Het^2alkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkyl radicals include 2-pyridylmethyl, 3- (4-thiazolyl)-propyl, and the like.

The term "Het^2alkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkylamino radicals include 4-pyridylmethylamino, 3 (2-furanyl)-propylamino, and the like.

The term "Het^2alkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkylthio radicals include 3-pyridylmethylthio, 3 (4-thiazolyl)-propylthio, and the like.

The term "Het^2amino" means Het^2 as defined herein, wherein a hydrogen atom on the Het^2 ring is replaced by a nitrogen. Het^2amino radicals include, for example, 4-thiazolylamino, 2-pyridylamino, and the like.

The term "Het^2oxy" means Het^2 as defined herein, wherein a hydrogen atom on the Het^2 ring is replaced by an oxygen. Het^2oxy radicals include, for example, 4-pyridyloxy, 5-quinolyloxy, and the like.

The term "Het^2oxycarbonyl" means an acyl radical derived from a carbonic acid represented by Het^2-O-COOH wherein Het^2 has the meaning given above.

The term "Het^1alkanoyl" is an acyl radical derived from a Het^1-substituted alkylcarboxylic acid wherein Het^1 has the meaning given above.

The term "Het^1alkoxycarbonyl" means an acyl group derived from Het^1-O-COOH wherein Het^1 is as defined above.

As used herein the term "oxa" refers to the group –O-.
As used herein the term "thia" refers to the group –S-.
As used herein the term "imino" refers to the group –NH-.
As used herein the term "cyano" refers to the group –CN.
As used herein the term "amidino" refers to the group –(HN=)C-NH_2.
As used herein the term "acetyl" refers to the group –(O=)C-CH_3.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

As used herein before, the term "one or more" covers the possibility of all the available C-atoms, where appropriate, to be substituted, preferably, one, two or three. When any variable, e.g. halogen or alkyl, occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term "compound(s) of the invention" or a similar term is meant to include the compounds of general formula I or formula II and any subgroup thereof. This term also refers to the compounds as depicted in Table A and B and their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, pro-drugs, esters and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. The compounds according to the invention may also exist in their tautomeric forms. Such forms, although not explicitly indicated in the compounds as described herein, are intended to be included within the scope of the present invention.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes pure stereoisomers as well as mixtures of stereoisomers, such as purified enantiomers/diasteromers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds per se, as well as any wholly or partially equilibrated mixtures thereof. The present invention covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

The term "pro-drug" as used herein means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug. The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th Ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13-15) describing pro-drugs generally is hereby incorporated. Pro-drugs of the compounds of the invention can be prepared by modifying functional groups present in said component in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent component. Typical examples of pro-drugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all

incorporated herein by reference. Pro-drugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*.

For therapeutic use, the "salts" of the compounds according to the invention, are those wherein the counterion is pharmaceutically or physiologically acceptable. The pharmaceutically acceptable salts of the analogues according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such a sarginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl–bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

The "pharmaceutically acceptable esters" of the compounds according to the invention refer to non-toxic esters, preferably the alkyl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or pentyl esters, of which the methyl ester is preferred. However, other esters such as phenyl-alkyl may be employed if desired.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute or a salt or pharmaceutical functional derivative thereof and a solvent. Such solvents for the purpose of the invention should not interfere with the biological activity of the solute.

Examples of solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutical acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, and acetic acid.

The term "pharmaceutically functional derivative" refers to any pharmaceutical acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation.

The compounds of the present invention may have the ability to crystallize in more than one form, a characteristic known as polymorphism. All polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature or pressure, or both, and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics that are known in the art such as x-ray diffraction patterns, solubility, and melting point.

In a preferred embodiment, the invention relates to a compound having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia and imino, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, cycloalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl,

aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^1oxy, Het^1alkyl, Het^1oxyalkyl, Het^1cycloalkyl, Het^1alkoxycarbonyl, Het^1oxycarbonyl, Het^1alkanoyl, Het^1alkyloxyalkyl, Het^1oxyalkylcarbonyl, Het^1alkyloxyalkylcarbonyl, Het^1aminocarbonyl, Het^1carbonyloxyalkyl, Het^1alkylcarbonyloxyalkyl, Het^1aryl, Het^1arylaminoalkoxy, Het^1arylamino, Het^1arylaminoalkyl, Het^1arylaminoalkylamino, Het^1aryloxy, Het^1aryloxyalkoxy, Het^1aryloxyalkyl, Het^1aryloxyalkylamino, Het^1aralkyl, Het^1aralkoxy, Het^1aralkylamino, Het^1aralkanoyl, Het^1aroyl, Het^1arylcarbonyl, Het^1aryloxycarbonyl, Het^1arylthiocarbonyl, Het^1aralkoxycarbonyl, Het^1arylalkylthiocarbonyl, Het^1aryloxyalkyl, Het^1arylthioalkyl, Het^1haloalkyl, Het^1aryloxycarbonylalkyl, Het^1aryloxyalkanoyl, Het^1aralkylcarbonyloxyalkyl, Het^1arylaminocarbonyl, Het^1aralkylaminocarbonyl, Het^1alkylaminoalkyl, Het^1aralkylaminoalkyl, Het^1alkanoylaminoalkyl, Het^1aroylaminoalkyl, Het^1aralkanoylaminoalkyl, Het^1alkyloxycarbonylaminoalkyl, Het^1aryloxycarbonylaminoalkyl, Het^1aralkoxycarbonylaminoalkyl, Het^1alkylaminocarbonylaminoalkyl, Het^1arylaminocarbonylaminoalkyl, Het^1aralkylaminocarbonylaminoalkyl, Het^1alkylaminoaryl, Het^1arylaminoaryl, Het^1aralkylaminoaryl, Het^1alkanoylaminoaryl, Het^1aroylaminoaryl, Het^1aralkanoylaminoaryl, Het^1alkyloxycarbonylaminoaryl, Het^1aryloxycarbonylaminoaryl, Het^1aralkoxycarbonylaminoaryl, Het^1alkylaminocarbonylaminoaryl, Het^1arylaminocarbonylaminoaryl, Het^1aralkylaminocarbonylaminoaryl, Het^1alkylaminoaralkyl, Het^1arylaminoaralkyl, Het^1aralkylaminoaralkyl, Het^1alkanoylaminoaralkyl, Het^1aroylaminoaralkyl, Het^1aralkanoylaminoaralkyl, Het^1alkyloxycarbonylaminoaralkyl, Het^1aryloxycarbonylaminoaralkyl, Het^1aralkoxycarbonylaminoaralkyl, Het^1alkylaminocarbonylaminoaralkyl, Het^1arylaminocarbonylaminoaralkyl, Het^1aralkylaminocarbonylaminoaralkyl, Het^2, Het^2oxy, Het^2alkyl, Het^2oxyalkyl, Het^2cycloalkyl, Het^2alkoxycarbonyl, Het^2oxycarbonyl, Het^2alkanoyl, Het^2alkyloxyalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aminocarbonyl, Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aryl, Het^2arylaminoalkoxy, Het^2arylamino, Het^2arylaminoalkyl, Het^2arylaminoalkylamino, Het^2aryloxy, Het^2aryloxyalkoxy, Het^2aryloxyalkyl,

Het^2aryloxyalkylamino, Het^2aralkyl, Het^2aralkoxy, Het^2aralkylamino, Het^2aralkanoyl, Het^2aroyl, Het^2arylcarbonyl, Het^2aryloxycarbonyl, Het^2arylthiocarbonyl, Het^2aralkoxycarbonyl, Het^2arylalkylthiocarbonyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2haloalkyl, Het^2aryloxycarbonylalkyl, Het^2aryloxyalkanoyl, Het^2aralkylcarbonyloxyalkyl, Het^2arylaminocarbonyl, Het^2aralkylaminocarbonyl, Het^2alkylaminoalkyl, Het^2aralkylaminoalkyl, Het^2alkanoylaminoalkyl, Het^2aroylaminoalkyl, Het^2aralkanoylaminoalkyl, Het^2alkyloxycarbonylaminoalkyl, Het^2aryloxycarbonylaminoalkyl, Het^2aralkoxycarbonylaminoalkyl, Het^2alkylaminocarbonylaminoalkyl, Het^2arylaminocarbonylaminoalkyl, Het^2aralkylaminocarbonylaminoalkyl, Het^2alkylaminoaryl, Het^2arylaminoaryl, Het^2aralkylaminoaryl, Het^2alkanoylaminoaryl, Het^2aroylaminoaryl, Het^2aralkanoylaminoaryl, Het^2alkyloxycarbonylaminoaryl, Het^2aryloxycarbonylaminoaryl, Het^2aralkoxycarbonylaminoaryl, Het^2alkylaminocarbonylaminoaryl, Het^2arylaminocarbonylaminoaryl, Het^2aralkylaminocarbonylaminoaryl, Het^2alkylaminoaralkyl, Het^2arylaminoaralkyl, Het^2aralkylaminoaralkyl, Het^2alkanoylaminoaralkyl, Het^2aroylaminoaralkyl, Het^2aralkanoylaminoaralkyl, Het^2alkyloxycarbonylaminoaralkyl, Het^2aryloxycarbonylaminoaralkyl, Het^2aralkoxycarbonylaminoaralkyl, Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is selected from the group comprising hydrogen, alkyl and halogen

In a more preferred embodiment, the invention provides a compound having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, and thia, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, cycloalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl,

arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^{1}oxy, Het^{1}alkyl, Het^{1}oxyalkyl, Het^{1}cycloalkyl, Het^{1}alkoxycarbonyl, Het^{1}oxycarbonyl, Het^{1}alkanoyl, Het^{1}alkyloxyalkyl, Het^{1}oxyalkylcarbonyl, Het^{1}alkyloxyalkylcarbonyl, Het^{1}aminocarbonyl, Het^{1}carbonyloxyalkyl, Het^{1}alkylcarbonyloxyalkyl, Het^{1}aryl, Het^{1}arylaminoalkoxy, Het^{1}arylamino, Het^{1}arylaminoalkyl, Het^{1}arylaminoalkylamino, Het^{1}aryloxy, Het^{1}aryloxyalkoxy, Het^{1}aryloxyalkyl, Het^{1}aryloxyalkylamino, Het^{1}aralkyl, Het^{1}aralkoxy, Het^{1}aralkylamino, Het^{1}aralkanoyl, Het^{1}aroyl, Het^{1}arylcarbonyl, Het^{1}aryloxycarbonyl, Het^{1}arylthiocarbonyl, Het^{1}aralkoxycarbonyl, Het^{1}arylalkylthiocarbonyl, Het^{1}aryloxyalkyl, Het^{1}arylthioalkyl, Het^{1}haloalkyl, Het^{1}aryloxycarbonylalkyl, Het^{1}aryloxyalkanoyl, Het^{1}aralkylcarbonyloxyalkyl, Het^{1}arylaminocarbonyl, Het^{1}aralkylaminocarbonyl, Het^{1}alkylaminoalkyl, Het^{1}aralkylaminoalkyl, Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl, Het^{1}aralkanoylaminoaryl, Het^{1}alkyloxycarbonylaminoaryl, Het^{1}aryloxycarbonylaminoaryl, Het^{1}aralkoxycarbonylaminoaryl, Het^{1}alkylaminocarbonylaminoaryl, Het^{1}arylaminocarbonylaminoaryl, Het^{1}aralkylaminocarbonylaminoaryl, Het^{1}alkylaminoaralkyl,

Het^{1}arylaminoaralkyl, Het^{1}aralkylaminoaralkyl, Het^{1}alkanoylaminoaralkyl, Het^{1}aroylaminoaralkyl, Het^{1}aralkanoylaminoaralkyl, Het^{1}alkyloxycarbonylaminoaralkyl, Het^{1}aryloxycarbonylaminoaralkyl, Het^{1}aralkoxycarbonylaminoaralkyl, Het^{1}alkylaminocarbonylaminoaralkyl, Het^{1}arylaminocarbonylaminoaralkyl, Het^{1}aralkylaminocarbonylaminoaralkyl, Het^2, Het^{2}oxy, Het^{2}alkyl, Het^{2}oxyalkyl, Het^{2}cycloalkyl, Het^{2}alkoxycarbonyl, Het^{2}oxycarbonyl, Het^{2}alkanoyl, Het^{2}alkyloxyalkyl, Het^{2}oxyalkylcarbonyl, Het^{2}alkyloxyalkylcarbonyl, Het^{2}aminocarbonyl, Het^{2}carbonyloxyalkyl, Het^{2}alkylcarbonyloxyalkyl, Het^{2}aryl, Het^{2}arylaminoalkoxy, Het^{2}arylamino, Het^{2}arylaminoalkyl, Het^{2}arylaminoalkylamino, Het^{2}aryloxy, Het^{2}aryloxyalkoxy, Het^{2}aryloxyalkyl, Het^{2}aryloxyalkylamino, Het^{2}aralkyl, Het^{2}aralkoxy, Het^{2}aralkylamino, Het^{2}aralkanoyl, Het^{2}aroyl, Het^{2}arylcarbonyl, Het^{2}aryloxycarbonyl, Het^{2}arylthiocarbonyl, Het^{2}aralkoxycarbonyl, Het^{2}arylalkylthiocarbonyl, Het^{2}aryloxyalkyl, Het^{2}arylthioalkyl, Het^{2}haloalkyl, Het^{2}aryloxycarbonylalkyl, Het^{2}aryloxyalkanoyl, Het^{2}aralkylcarbonyloxyalkyl, Het^{2}arylaminocarbonyl, Het^{2}aralkylaminocarbonyl, Het^{2}alkylaminoalkyl, Het^{2}aralkylaminoalkyl, Het^{2}alkanoylaminoalkyl, Het^{2}aroylaminoalkyl, Het^{2}aralkanoylaminoalkyl, Het^{2}alkyloxycarbonylaminoalkyl, Het^{2}aryloxycarbonylaminoalkyl, Het^{2}aralkoxycarbonylaminoalkyl, Het^{2}alkylaminocarbonylaminoalkyl, Het^{2}arylaminocarbonylaminoalkyl, Het^{2}aralkylaminocarbonylaminoalkyl, Het^{2}alkylaminoaryl, Het^{2}arylaminoaryl, Het^{2}aralkylaminoaryl, Het^{2}alkanoylaminoaryl, Het^{2}aroylaminoaryl, Het^{2}aralkanoylaminoaryl, Het^{2}alkyloxycarbonylaminoaryl, Het^{2}aryloxycarbonylaminoaryl, Het^{2}aralkoxycarbonylaminoaryl, Het^{2}alkylaminocarbonylaminoaryl, Het^{2}arylaminocarbonylaminoaryl, Het^{2}aralkylaminocarbonylaminoaryl, Het^{2}alkylaminoaralkyl, Het^{2}arylaminoaralkyl, Het^{2}aralkylaminoaralkyl, Het^{2}alkanoylaminoaralkyl, Het^{2}aroylaminoaralkyl, Het^{2}aralkanoylaminoaralkyl, Het^{2}alkyloxycarbonylaminoaralkyl, Het^{2}aryloxycarbonylaminoaralkyl, Het^{2}aralkoxycarbonylaminoaralkyl, Het^{2}alkylaminocarbonylaminoaralkyl, Het^{2}arylaminocarbonylaminoaralkyl, Het^{2}aralkylaminocarbonylaminoaralkyl,

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen, fluor or methyl.

In another more preferred embodiment a compound is provided having the general formula I or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, and thia or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen and cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, aryl, cycloalkyl, aralkyl, cycloalkylalkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, alkylaminocarbonyl, alkylaminoalkyl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxyalkylamino, aralkylamino, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyol, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen, fluor or methyl.

In a particularly preferred embodiment, a compound according to the invention is a compound having the general formula I or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia

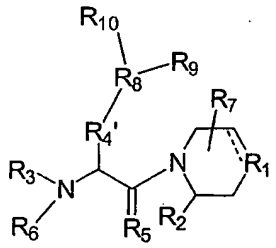
wherein R^2 is selected from the group comprising hydrogen and cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, aryl, cycloalkyl, aralkyl, cycloalkylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, aralkylamino, aralkylaminoalkyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen or fluor.

In a more preferred embodiment, the compounds of the invention have general formula II as represented below,



formula II

wherein $R_1, R_2, R_3, R_5, R_6, R_7$ have the same meaning as indicated herein,

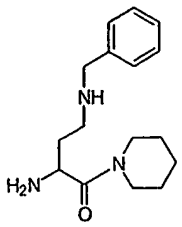
wherein $R_{4'}, R_8, R_9, R_{10}$ are selected from the group comprising nitrogen, hydrogen, oxyalkyl, alkyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkylamino, aminoalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, aminoalkanoyl, aminocarbonyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl,

aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^{1}oxy, Het^{1}alkyl, Het^{1}oxyalkyl, Het^{1}cycloalkyl, Het^{1}alkoxycarbonyl, Het^{1}oxycarbonyl, Het^{1}alkanoyl, Het^{1}alkyloxyalkyl, Het^{1}oxyalkylcarbonyl, Het^{1}alkyloxyalkylcarbonyl, Het^{1}aminocarbonyl, Het^{1}carbonyloxyalkyl, Het^{1}alkylcarbonyloxyalkyl, Het^{1}aryl, Het^{1}arylaminoalkoxy, Het^{1}arylamino, Het^{1}arylaminoalkyl, Het^{1}arylaminoalkylamino, Het^{1}aryloxy, Het^{1}aryloxyalkoxy, Het^{1}aryloxyalkyl, Het^{1}aryloxyalkylamino, Het^{1}aralkyl, Het^{1}aralkoxy, Het^{1}aralkylamino, Het^{1}aralkanoyl, Het^{1}aroyl, Het^{1}arylcarbonyl, Het^{1}aryloxycarbonyl, Het^{1}arylthiocarbonyl, Het^{1}aralkoxycarbonyl, Het^{1}arylalkylthiocarbonyl, Het^{1}aryloxyalkyl, Het^{1}arylthioalkyl, Het^{1}haloalkyl, Het^{1}aryloxycarbonylalkyl, Het^{1}aryloxyalkanoyl, Het^{1}aralkylcarbonyloxyalkyl, Het^{1}arylaminocarbonyl, Het^{1}aralkylaminocarbonyl, Het^{1}alkylaminoalkyl, Het^{1}aralkylaminoalkyl, Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl, Het^{1}aralkanoylaminoaryl, Het^{1}alkyloxycarbonylaminoaryl, Het^{1}aryloxycarbonylaminoaryl, Het^{1}aralkoxycarbonylaminoaryl, Het^{1}alkylaminocarbonylaminoaryl, Het^{1}arylaminocarbonylaminoaryl, Het^{1}aralkylaminocarbonylaminoaryl, Het^{1}alkylaminoaralkyl, Het^{1}arylaminoaralkyl, Het^{1}aralkylaminoaralkyl, Het^{1}alkanoylaminoaralkyl, Het^{1}aroylaminoaralkyl, Het^{1}aralkanoylaminoaralkyl, Het^{1}alkyloxycarbonylaminoaralkyl, Het^{1}aryloxycarbonylaminoaralkyl, Het^{1}aralkoxycarbonylaminoaralkyl, Het^{1}alkylaminocarbonylaminoaralkyl, Het^{1}arylaminocarbonylaminoaralkyl,

Het^{1}aralkylaminocarbonylaminoaralkyl, Het^2, Het^{2}oxy, Het^{2}alkyl, Het^{2}oxyalkyl, Het^{2}cycloalkyl, Het^{2}alkoxycarbonyl, Het^{2}oxycarbonyl, Het^{2}alkanoyl, Het^{2}alkyloxyalkyl, Het^{2}oxyalkylcarbonyl, Het^{2}alkyloxyalkylcarbonyl, Het^{2}aminocarbonyl, Het^{2}carbonyloxyalkyl, Het^{2}alkylcarbonyloxyalkyl, Het^{2}aryl, Het^{2}arylaminoalkoxy, Het^{2}arylamino, Het^{2}arylaminoalkyl, Het^{2}arylaminoalkylamino, Het^{2}aryloxy, Het^{2}aryloxyalkoxy, Het^{2}aryloxyalkyl, Het^{2}aryloxyalkylamino, Het^{2}aralkyl, Het^{2}aralkoxy, Het^{2}aralkylamino, Het^{2}aralkanoyl, Het^{2}aroyl, Het^{2}arylcarbonyl, Het^{2}aryloxycarbonyl, Het^{2}arylthiocarbonyl, Het^{2}aralkoxycarbonyl, Het^{2}arylalkylthiocarbonyl, Het^{2}aryloxyalkyl, Het^{2}arylthioalkyl, Het^{2}haloalkyl, Het^{2}aryloxycarbonylalkyl, Het^{2}aryloxyalkanoyl, Het^{2}aralkylcarbonyloxyalkyl, Het^{2}arylaminocarbonyl, Het^{2}aralkylaminocarbonyl, Het^{2}alkylaminoalkyl, Het^{2}aralkylaminoalkyl, Het^{2}alkanoylaminoalkyl, Het^{2}aroylaminoalkyl, Het^{2}aralkanoylaminoalkyl, Het^{2}alkyloxycarbonylaminoalkyl, Het^{2}aryloxycarbonylaminoalkyl, Het^{2}aralkoxycarbonylaminoalkyl, Het^{2}alkylaminocarbonylaminoalkyl, Het^{2}arylaminocarbonylaminoalkyl, Het^{2}aralkylaminocarbonylaminoalkyl, Het^{2}alkylaminoaryl, Het^{2}arylaminoaryl, Het^{2}aralkylaminoaryl, Het^{2}alkanoylaminoaryl, Het^{2}aroylaminoaryl, Het^{2}aralkanoylaminoaryl, Het^{2}alkyloxycarbonylaminoaryl, Het^{2}aryloxycarbonylaminoaryl, Het^{2}aralkoxycarbonylaminoaryl, Het^{2}alkylaminocarbonylaminoaryl, Het^{2}arylaminocarbonylaminoaryl, Het^{2}aralkylaminocarbonylaminoaryl, Het^{2}alkylaminoaralkyl, Het^{2}arylaminoaralkyl, Het^{2}aralkylaminoaralkyl, Het^{2}alkanoylaminoaralkyl, Het^{2}aroylaminoaralkyl, Het^{2}aralkanoylaminoaralkyl, Het^{2}alkyloxycarbonylaminoaralkyl, Het^{2}aryloxycarbonylaminoaralkyl, Het^{2}aralkoxycarbonylaminoaralkyl, Het^{2}alkylaminocarbonylaminoaralkyl, Het^{2}arylaminocarbonylaminoaralkyl, Het^{2}aralkylaminocarbonylaminoaralkyl,

and wherein $R_{4'}$, R_8, R_9, R_{10} are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2.

In a specific embodiment, a compound is provided being N^1-benzyl-4-oxo-4-(1-piperidinyl)-1,3(S)-butanediamine as indicated with formula IV according to the specification given below. This particular compound corresponding to formula IV as represented below is also referred to as KS IV.7.



formula IV

The potency of the compounds to inhibit serine type dipeptidyl peptidases according to the present invention are expressed as IC_{50} value. The "IC_{50} value" is defined as the concentration of a compound, which causes the enzyme activity to decrease with 50 % under assay conditions.

The compounds according to the present invention all preferably inhibit DPP activity, exhibiting relatively high activity at relatively low concentrations, as indicated by low IC_{50} values. Preferably, the IC_{50} values of the compounds according to the present invention are lower than 100 µM, more preferred lower than 10µM, even more preferred lower than 0.1 µM.

According to another preferred embodiment, some of the presented compounds are very useful to differentiate between DPP II and DPP IV activity in biological systems, since some of these compounds are highly specific and selective for DPPII inhibitory activity than currently available inhibitors. DPP II and DPP IV both preferentially release N-terminal dipeptide moieties (Xaa-Pro- or Xaa-Ala-) from some oligopeptides or proteins. DPP IV and DPP II share substrate specificity, and differentiating between these acitivites is generally a challenging and difficult task.

In an example, the compound KS IV.7 as defined above is a particularly active and selective DPPII inhibitor. This compound has an IC_{50} value of 0.00203 µM for DPPII. For comparison, the IC_{50} value of this compound towards DPP IV comprises 247 µM. This compound thus has a particularly high selectivity of for DPPII, and is particularly suitable for in applications wherein a differentiation is required between DPP II and DPP IV activity.

In a preferred embodiment, the invention thus relates to compounds for use as a medicament. The compounds according to the present invention can be used in the treatment

of pathological states associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase. In a preferred embodiment, said compounds according to the invention can be used in the treatment of diseases associated with excessive, impaired or unbalanced activity of DPPIV. In another preferred embodiment, said compounds according to the invention can be used in the treatment of diseases associated with excessive, impaired or unbalanced activity of DPPII.

According to a further aspect the invention also relates to the use of the compounds according to the invention in the preparation of a medicament for inhibiting the activity of a serine type dipeptidyl peptidase. In a preferred embodiment, the invention also relates to the use of said compounds according to the invention in the preparation of a medicament for inhibiting the activity of DPPIV. In another preferred embodiment, the invention also relates to the use of said compounds according to the invention in the preparation of a medicament for inhibiting the activity of DPPII.

Preferably, the invention also relates to the use of the compounds according to the invention in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase. In a preferred embodiment, the invention also relates to the use of said compounds according to the invention in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of DPPIV. In another preferred embodiment, the invention also relates to the use of said compounds according to the invention in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of DPPII. Such medicaments are then specifically intended for treatment and prophylaxis of the conditions listed below. Starting from the available information on the correlation between a particular serine type dipeptidyl peptidase activity and various disease states the skilled person will be able to define therapeutic utilities for the inhibitory compounds of the invention. While not being limited thereby, the compounds of the present invention are believed useful for the treatment of a variety of metabolic, neuroendocrine, gastrointestinal, viral, and inflammatory diseases, including, but not limited to, diabetes, obesity, hyperlipidemia, dermatological or mucous membrane disorders, psoriasis, intestinal distress, constipation, (auto)immune disorders such as encephalomyelitis, complement mediated disorders such as glomerulonepritis, lipodystrophy, and tissue damage, psychosomatic, depressive, and neuropsychiatric disease such as anxiety, depression, insomnia, schizophrenia, epilepsy,

spasm, and chronic pain, HIV infection, allergies, inflammation, arthritis, transplant rejection, high blood pressure, congestive heart failure, tumors, and stress-induced abortions.

The invention also relates to the diagnostic use of the compounds. In another preferred embodiment, the compounds according to the present invention can be used in diagnostic and research methods such as fluorescence, purification and radio-assays, imaging, *in situ* histochemical and cytochemical staining.

In particular, the present invention relates to the use of a compound according to the invention in purification procedures of serine type peptidases and preferably of dipeptidyl peptidases. The said compounds can be immobilized to a suitable matrix or used as a competitor to elute bound enzyme from a matrix containing an immobllized compound.

The present invention also includes compounds, which have been modified without abolishing the reactivity with the active site. Examples of such modifications are the incorporation of radioactive labels such as Iodine^{125}, or non-radioactive labels such as biotin or a fluorophore. The incorporation of a (radioactive) label is useful in diagnostic methods using the modulating compounds. Labelled compounds can be used essentially in the same type of appli cations as labelled monoclonal antibodies, e.g. fluorescence and radioassays, cytofluorimetry, fluorenscence activated cell sorting, etc ... The principles of such techniques are well known to the person skilled in the art.

The DPP inhibitors described above which form complexes with dipeptidyl peptidases are therefore suitable for diagnostic applications such as imaging and histochemical staining of DPP. This requires the introduction of a radioisotope, e.g. iodine, or a fluorescent or other type of reporter group. Because of their small size they are expected to penetrate tissue more easily as, for example, antibodies. Formulations of the compounds to be used in diagnostic applications are also part of this invention.

DPP activities can interfere with certain assays by cleaving the substrate used in the test and thereby giving either false positive (when a chromogenic substrate is cleaved) or false negative results (when a peptide is degraded). The inhibitors of this invention can be used to inactivate a contaminating DPP activity before carrying on with the analysis.

In cytochemistry and histochemistry labeled inhibitors can be used to directly visualize the cellular distribution of the target protease (DPP). The label can be fluorescent for fluorescence microscopy, radioactive for autoradiography, or electron dense for electron microscopy. The target structures can be whole cells, cells fixed onto slides or sections through solid tissue. A useful modification of these techniques is to use an indirect ("sandwich") assay employing the specific high affinity interaction between biotin and avidin (reviewed in Methods in Enzymology, vol. 184, 1990).

For imaging of tumours expressing high amounts of the target protease (DPP), inhibitors labeled with a suitable isotope (e.g. I^{125} or I^{131}) can be injected and after clearing of the excess inhibitor from the circulation, the tumour can be visualized by radio-scintigraphy.

The compounds of the invention which form a stable adduct with DPP may be used as a tool for diagnosing of the above cited disease states.

Furthermore, the present invention also encompasses pharmaceutical compositions prepared for storage and subsequent administration, which have a therapeutically effective amount of one or more compounds of the invention and a pharmaceutically acceptable excipient, carrier or diluent. Such pharmaceutical preparations are intended for the treatment and prophylaxis of the above conditions.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

Acceptable carriers and diluents are well known and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). Preservatives, stabilizers, dyes and flavoring agents may be provided in the pharmaceutical compositions. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition antioxidants and suspending agents may be used.

The compositions of this invention may be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions or suspensions for injectable administration; aerosols; unguents for topical administration. If desired, absorption enhancing preparations (e.g. liposomes) or other appropriate delivery systems may be used. The amount of the active substances(s) in a dosage unit may vary between 0.01 mg and 1 g.

Formulations of the present invention include those especially formulated for oral, buccal, parental, transdermal, inhalation, intranasal, transmucosal, implant, or rectal administration in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

Among the variety of administrations, oral administration typically is preferred. For oral administration tablets, capsules, and caplets may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, and/or wetting agents. Non-limiting examples of binding agents include syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, or polyvinylpyrrolidone (PVP). Non-limiting examples of fillers include, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol. Non-limiting examples of lubricants include, for example, magnesium sterate, stearic acid, talc, polyethylene glycol or silica. Non-limiting examples of disintegrants include, for example, potato starch or sodium starch glycollate. A non-limiting example of a wetting agent includes sodium lauryl sulfate. The tablets additionally may be coated according to methods known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives. Non-limiting examples of such additives include suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum sterate gel or hydrogenated edible fats. Additionally, emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol my be included. Further, preservatives such as methyl or

propyl p-hydroxybenzoates or sorbic acid, may be incorporated into the preparation. Such preparations may also be formulated as suppositories, for example, containing conventional suppository bases such as cocoa butter or other glycerides.

Additionally, formulations of the present invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, for example, sterile, pyrogen-free water, before use.

The formulations according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly, or by intramuscular injection. Accordingly, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials, such as an emulsion in an acceptable oil, ion exchange resins, or as sparingly soluble derivatives, such as a sparingly soluble salt.

The compounds of the present invention may be used in combination with one or more other therapeutic or diagnostic agents in the treatment, prevention, suppression, amelioration, or diagnosing of diseases or conditions for which compounds of the invention or the other agents may have utility, where the combination of the drugs together are safer or more effective than either agent alone.

Such other agents may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other agents, a pharmaceutical composition in unit dosage form containing such other agents and the compound of the invention. is preferred. However, the combination therapy may also include therapies in which the compound of the invention. and one or more other agents are administered on different overlapping schedules.

It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be

used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the invention.

Examples of other active ingredients that may be administered in combination with a compound of the present invention, and either administered separately or in the same pharmaceutical composition, include, but are not limited to other dipeptidyl peptidase inhibitors. In a preferred embodiment, certain compounds of the invention can be combined with each other such that synergetic inhibiting effects are obtained.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other agents that are used in the treatment/prevention/suppression or amelioration of diseases or conditions for which compounds of the present invention are useful.

The weight ratio of a compound of the present invention to a second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:I to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The dosage for the compounds of the present invention can range broadly depending upon the desired effects and the therapeutic indication. The pharmaceutical compositions of this invention can be administered to humans in dosage ranges specific for each compound comprised in said compositions. The dosage for the compounds of the present invention can range broadly depending upon the desired effects and the therapeutic indication.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain certain amounts of a compound of the present invention depending on the condition being treated, the route of administration, and the age, weight and condition of the patient. Examples of such amounts include the formulation containing about 0.1 to about 99.9% active ingredient. Preferred unit dosage formulations are those containing a predetermined dose, such as a daily dose, or an appropriate fraction thereof, of an active ingredient. Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

In another embodiment, the invention relates to a method of treatment of diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase comprising administrating to an individual in need of such treatment a pharmaceutical composition according to the invention. The term "individual," as used herein refers to an animal, preferably a mammal, and most preferably a human, who has been the object of treatment, observation or experiment.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment.

It will be understood, however, that specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific analogue employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

In another aspect, the present invention relates to a method for inhibiting the activity of a serine type dipeptidyl peptidase by administering a compound according to the present invention. The present invention relates to a method for *in vitro* inhibition of the activity of a serine type dipeptidyl peptidase by means of administering a suitable concentration of a compound of the invention. Such method is in particular useful when a DPP enzyme inactivates a peptide prior to measurement thereof in a peptide assay. The compounds of the

invention can be used to inhibit the degradation of the peptide substrate by the enzyme in such assay. The compounds of the invention are also useful in a method for *ex vivo* inhibition of the activity of a serine type dipeptidyl peptidase, such as the treatment outside the body of cells and organs for transplantation in order to avoid rejection thereof by the recipient body. The method comprises administering a suitable concentration of a compound according to the invention. Furthermore, the compounds of the invention can be used in a method for *in vivo* inhibiting of the activity of a serine type dipeptidyl peptidase by means of administering to a living organism a suitable amount of a compound of the invention.

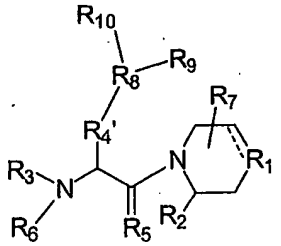
In a further embodiment, the present invention relates to kits comprising a compound according to the invention. In a more preferred embodiment, the invention further provides for assay kits for assaying the inhibition of the activity of a serine type dipeptidyl peptidase comprising a compound according to the invention and means to detect said inhibition.

The present invention will be further elucidated with reference to the following examples which are only given for illustration purposes and are in no way intended to limit the invention.

Examples

Example 1 Non-limiting examples of compounds according to the invention

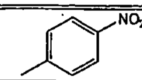
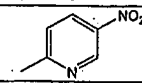
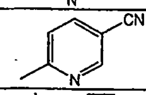
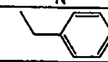
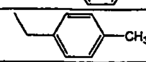
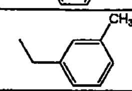
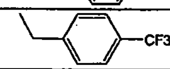
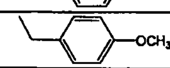
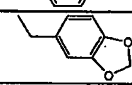
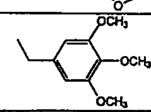
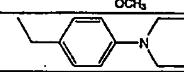
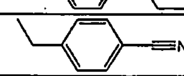
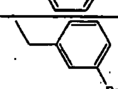
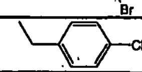
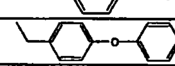
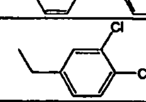
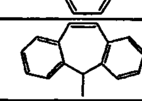
Non-limiting examples of compounds according to the invention and having general formula II are listed in Table A, wherein reference is made to R_1, R_2, R_3, R_4', R_5, R_6, R_7, R_8, R_9, R_{10}.

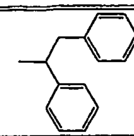
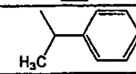
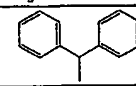
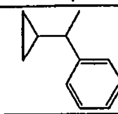
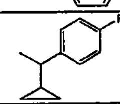
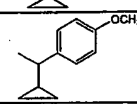
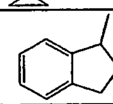
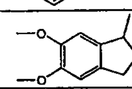
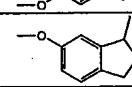
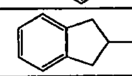
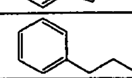
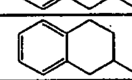
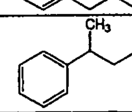
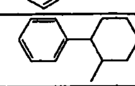
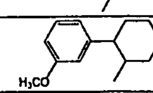
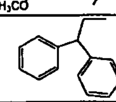


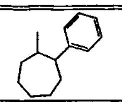
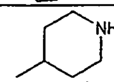
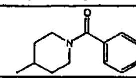
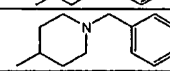
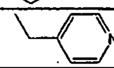
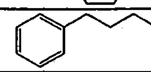
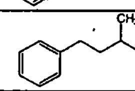
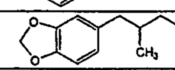
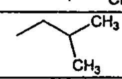
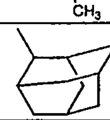
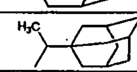
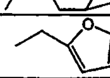
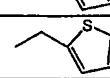
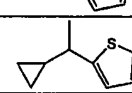
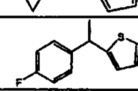
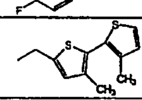
formula II

Table A

R_1	R_2	R_3	R_4'	R_5	R_6	R_7	R_8	R_9	R_{10}
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	-H

$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2-$	O	-H	-H	-N-	-H	

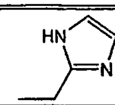
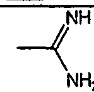
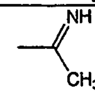
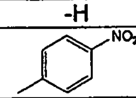
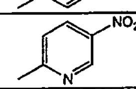
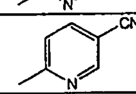
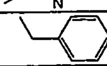
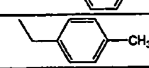
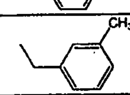
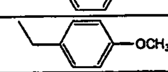
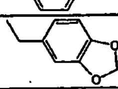
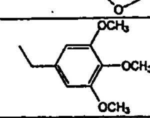
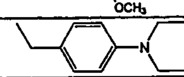
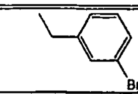
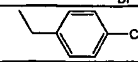
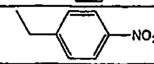
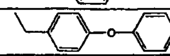
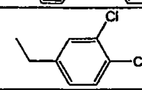
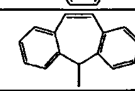
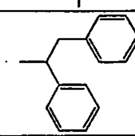
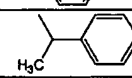
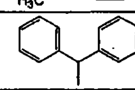
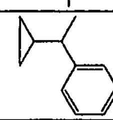
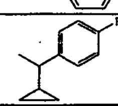
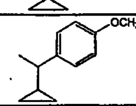
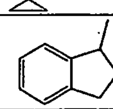
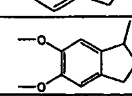
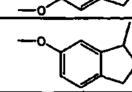
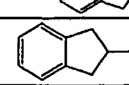
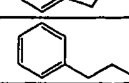
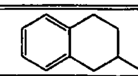
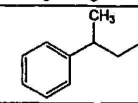
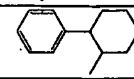
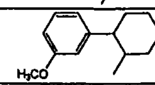
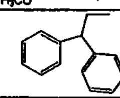
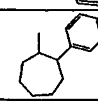
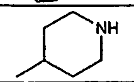
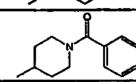
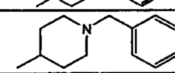
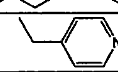
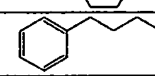
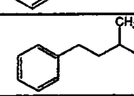
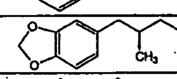
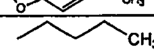
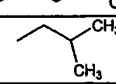
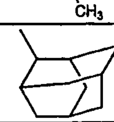
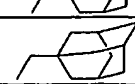
-CH$_2$-	-H	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-H	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-H	-H	-CH$_2$-	O	-H	-H	-N-	-H	

Table A (continued)

R_1	R_2	R_3	R_4'	R_5	R_6	R_7	R_8	R_9	R_{10}
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$-	O	-H	-H	-N-	-H	

-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	
-CH2-	-CN	-H	-CH2-	O	-H	-H	-N-	-H	

$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	

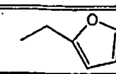
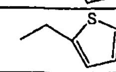
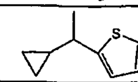
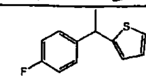
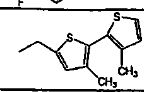
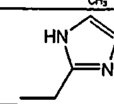
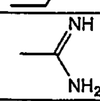
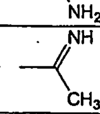
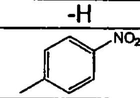
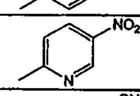
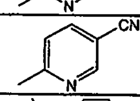
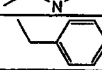
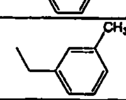
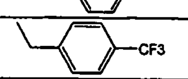
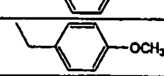
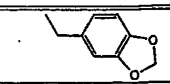
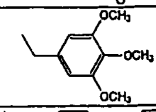
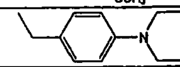
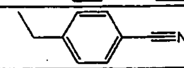
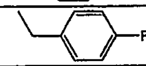
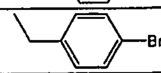
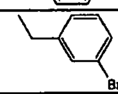
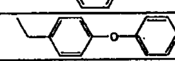
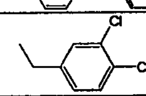
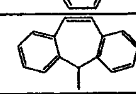
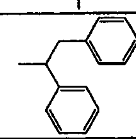
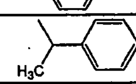
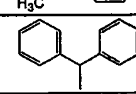
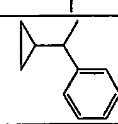
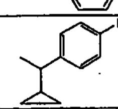
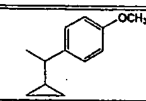
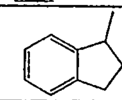
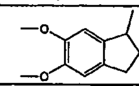
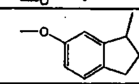
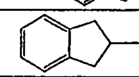
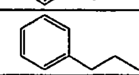
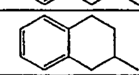
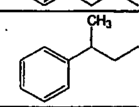
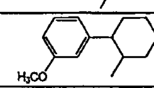
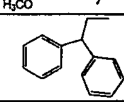
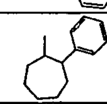
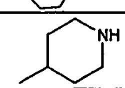
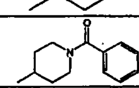
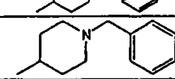
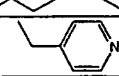
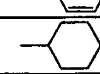
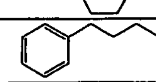
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2-$	O	-H	-H	-N-	-H	

Table A (continued)

R_1	R_2	R_3	R_4'	R_5	R_6	R_7	R_8	R_9	R_{10}
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

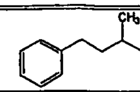
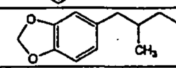
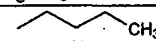
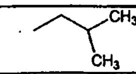
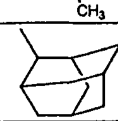
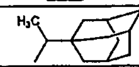
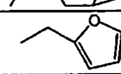
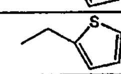
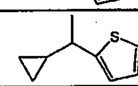
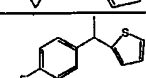
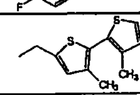
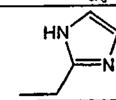
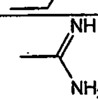
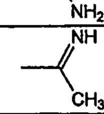
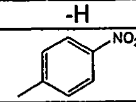
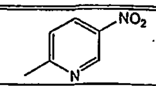
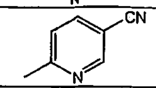
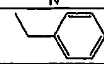
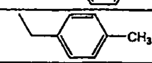
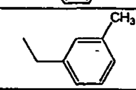
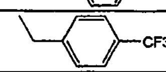
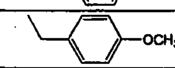
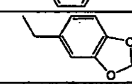
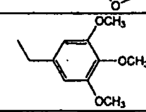
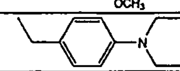
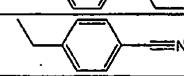
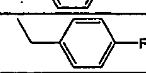
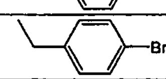
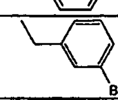
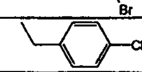
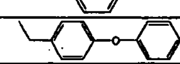
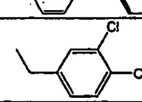
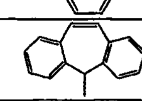
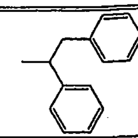
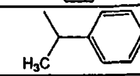
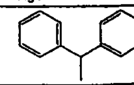
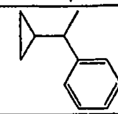
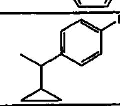
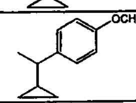
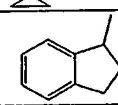
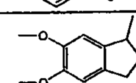
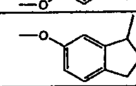
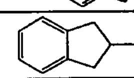
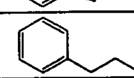
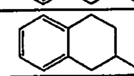
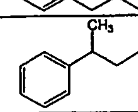
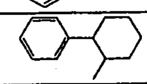
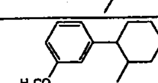
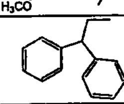
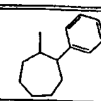
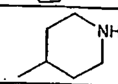
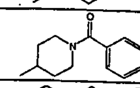
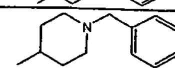
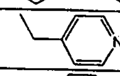
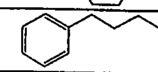
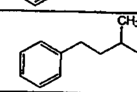
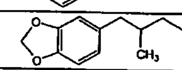
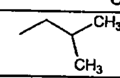
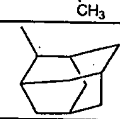
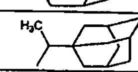
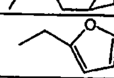
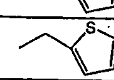
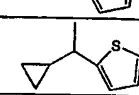
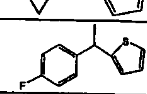
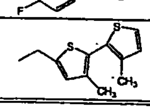
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	
-CH2-	-H	-H	-CH2CH2-	O	-H	-H	-N-	-H	

Table A (continued)

R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
-CH2-	-CN	-H	-CH2CH2-	O	-H	-H	-N-	-H	-H
-CH2-	-CN	-H	-CH2CH2-	O	-H	-H	-N-	-H	

$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-H	-H	-N-	-H	

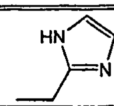
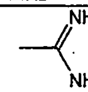
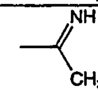
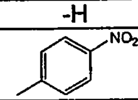
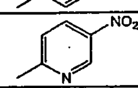
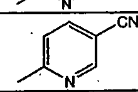
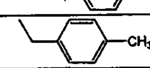
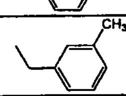
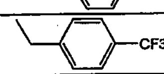
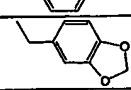
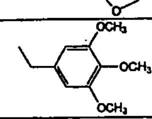
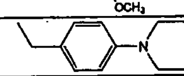
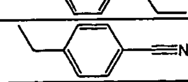
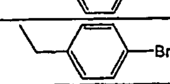
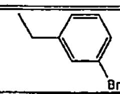
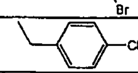
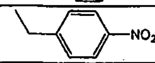
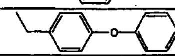
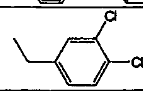
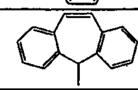
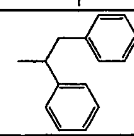
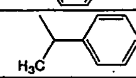
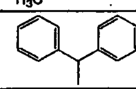
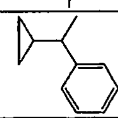
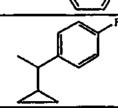
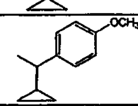
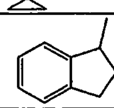
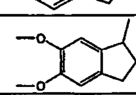
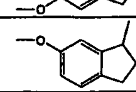
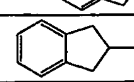
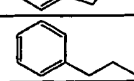
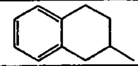
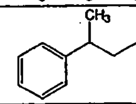
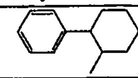
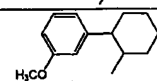
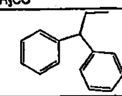
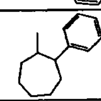
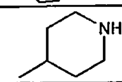
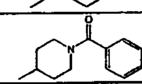
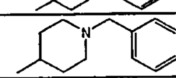
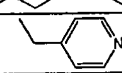
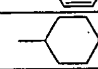
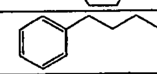
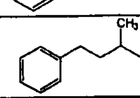
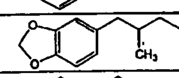
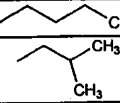
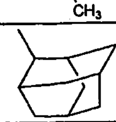
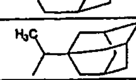
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$-	O	-H	-H	-N-	-H	
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$-	O	-H	-H	-N-	-H	

Table A (continued)

R_1	R_2	R_3	R_4'	R_5	R_8	R_{10}	R_7	R_6	R_9
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-	-H	-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H

-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H
-CH_2-	-H	-H	-$CH_2CH_2CH_2$-	O	-N-		-H	-H	-H

-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-H	-H	-CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H

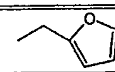
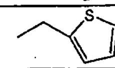
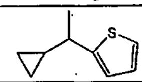
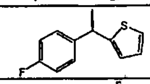
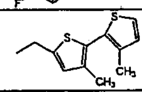
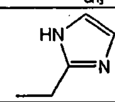
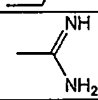
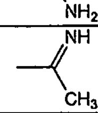
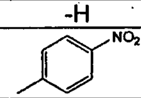
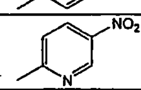
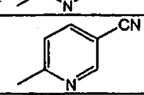
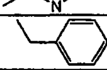
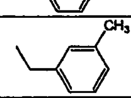
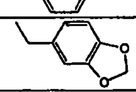
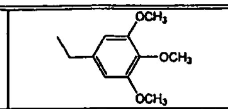
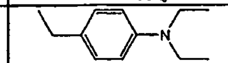
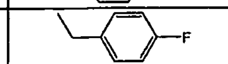
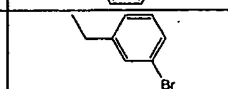
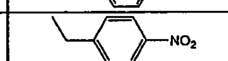
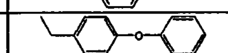
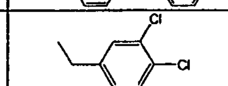
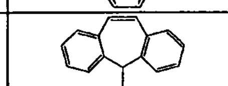
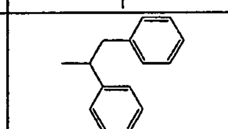
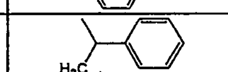
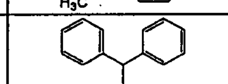
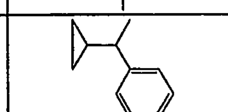
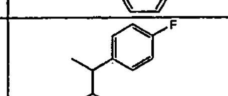
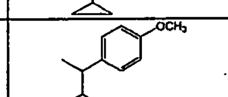
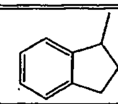
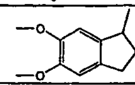
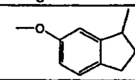
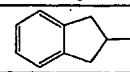
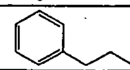
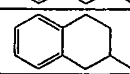
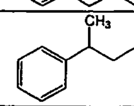
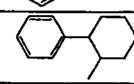
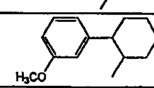
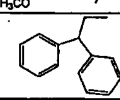
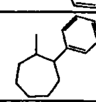
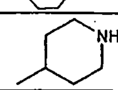
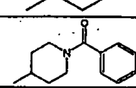
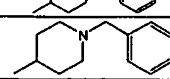
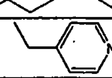
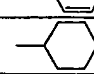
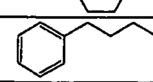
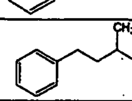
R1	R2	R3	R4	R5	R8	R10	R7	R6	R9
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

Table A (continued)

R_1	R_2	R_3	R_4	R_5	R_8	R_{10}	R_7	R_6	R_9
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-	-H	-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

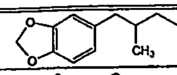
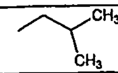
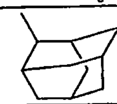
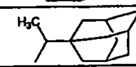
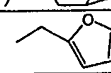
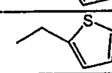
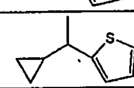
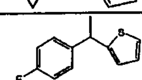
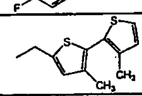
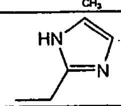
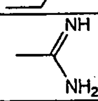
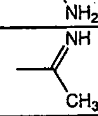
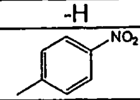
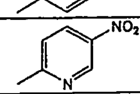
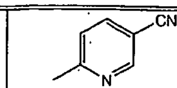
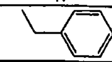
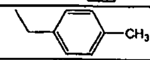
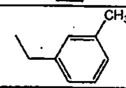
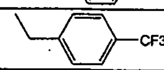
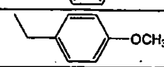
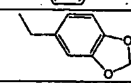
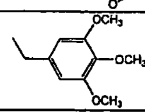
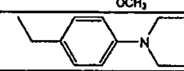
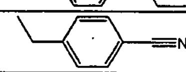
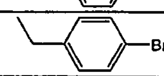
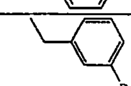
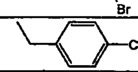
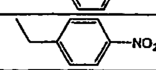
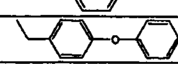
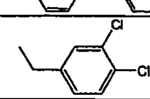
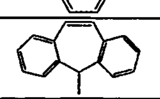
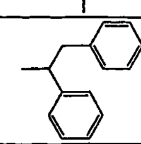
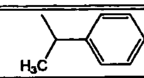
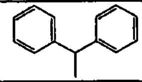
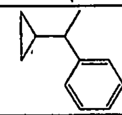
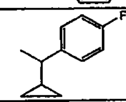
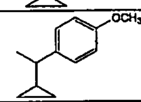
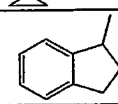
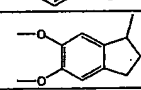
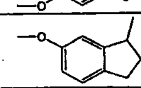
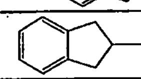
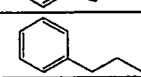
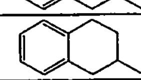
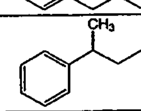
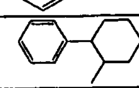
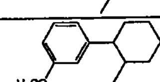
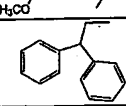
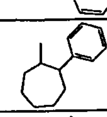
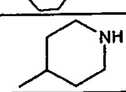
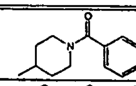
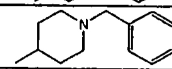
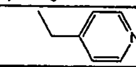
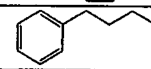
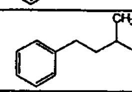
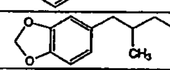
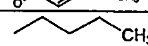
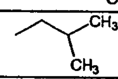
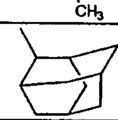
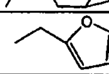
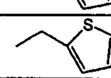
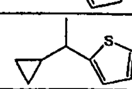
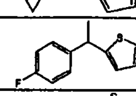
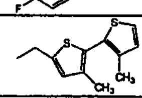
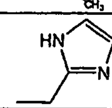
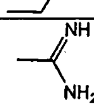
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-CN	-H	-CH2CH2CH2-	O	-N-		-H	-H	-H

Table A (continued)

R1	R2	R3	R4	R5	R8	R10	R7	R6	R9
-CH2-	-H	-H	-CH2CH2CH2CH2-	O	-N-	-H	-H	-H	-H
-CH2-	-H	-H	-CH2CH2CH2CH2-	O	-N-		-H	-H	-H
-CH2-	-H	-H	-CH2CH2CH2CH2-	O	-N-		-H	-H	-H

$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

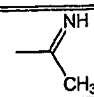
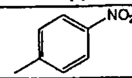
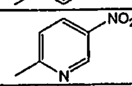
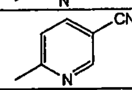
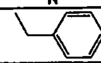
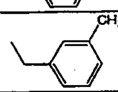
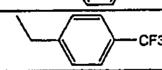
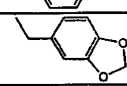
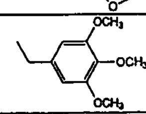
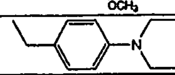
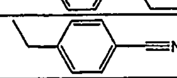
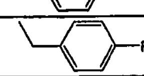
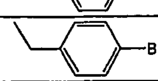
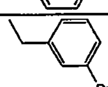
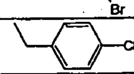
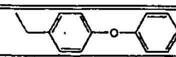
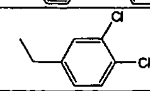
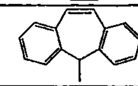
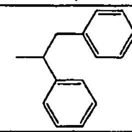
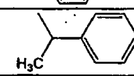
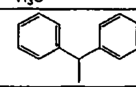
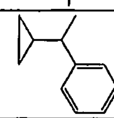
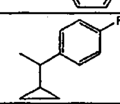
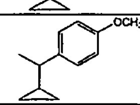
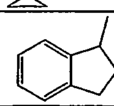
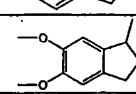
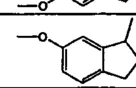
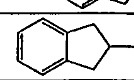
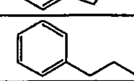
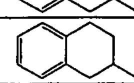
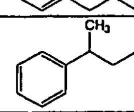
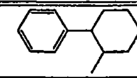
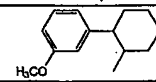
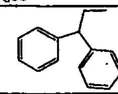
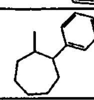
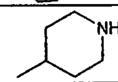
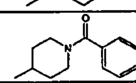
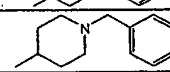
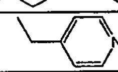
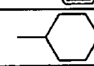
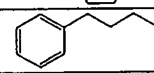
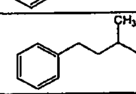
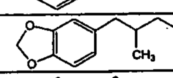
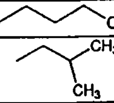
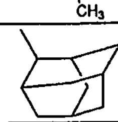
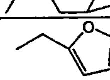
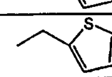
-CH₂-	-H	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

Table A (continued)

R_1	R_2	R_3	R_4'	R_5	R_8	R_{10}	R_7	R_6	R_9
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-	-H	-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H
-CH$_2$-	-CN	-H	-CH$_2$CH$_2$CH$_2$CH$_2$-	O	-N-		-H	-H	-H

$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

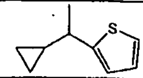
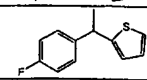
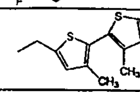
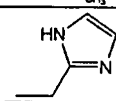
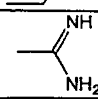
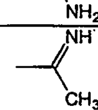
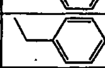
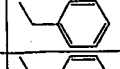
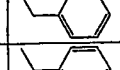
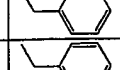
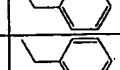
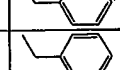
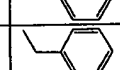
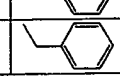
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2CH_2CH_2-$	O	-N-		-H	-H	-H

Table A (continued)

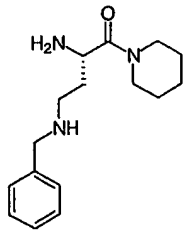
R_1	R_2	R_3	R_4'	R_5	R_8	R_{10}	R_7	R_6	R_9
$-CH_2-$	-H	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-CN	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_3$
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_2CH_3$
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_3$
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_2CH_3$
$-CH_2-$	-H	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_3$
$-CH_2-$	-H	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_2CH_3$
$-CH_2-$	-CN	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_3$
$-CH_2-$	-CN	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	-H	$-CH_2CH_3$
$-CH_2-$	-H	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_3$	-H
$-CH_2-$	-H	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_2CH_3$	-H

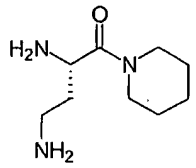
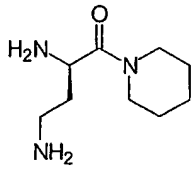
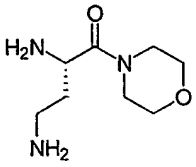
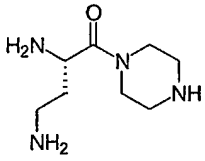
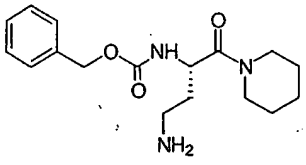
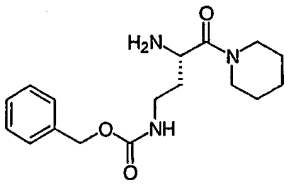
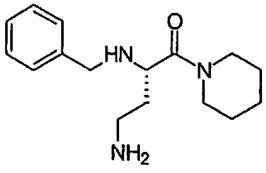
$-CH_2-$	-CN	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_3$	-H
$-CH_2-$	-CN	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_2CH_3$	-H
$-CH_2-$	-H	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_3$	$-CH_3$
$-CH_2-$	-H	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_2CH_3$	$-CH_2CH_3$
$-CH_2-$	-CN	$-CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_3$	$-CH_3$
$-CH_2-$	-CN	$-CH_2CH_3$	$-CH_2CH_2-$	O	-N-		-H	$-CH_2CH_3$	$-CH_2CH_3$
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-N-		-F	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-N-		$-CH_3$	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-N-		-F	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-N-		$-CH_3$	-H	-H
$-CH_2-$	-H	-H	$-CH_2CH_2-$	O	-N-		-Cl	-H	-H
$-CH_2-$	-CN	-H	$-CH_2CH_2-$	O	-N-		-Cl	-H	-H

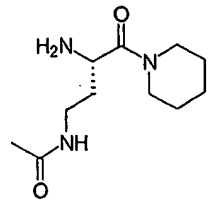
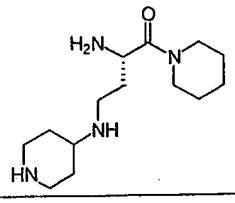
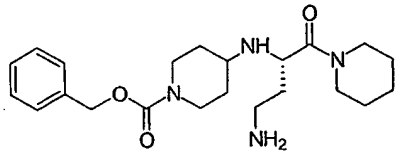
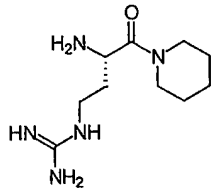
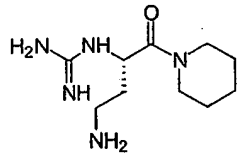
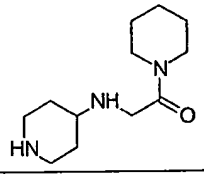
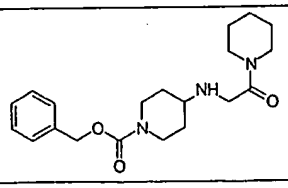
Example 2 Specific examples of compounds according to the invention

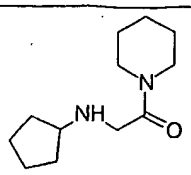
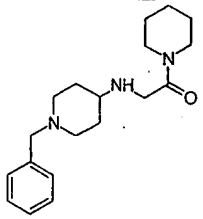
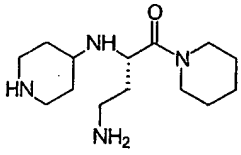
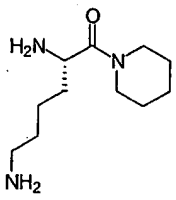
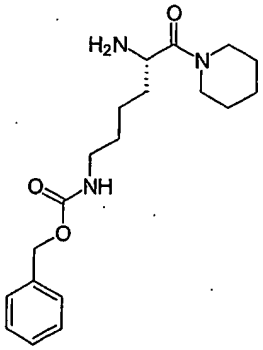
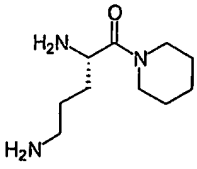
The present example illustrates some specific examples of compounds according to the invention (Table B). Also indicated are the IC_{50} values of the indicated compounds for DPPII and DPPIV.

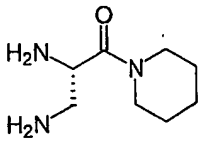
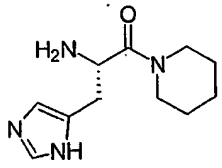
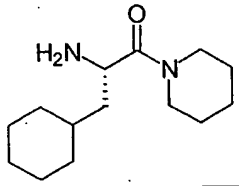
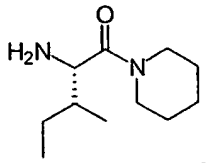
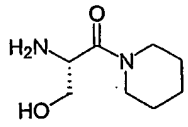
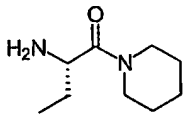
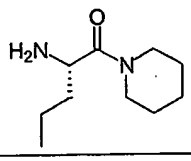
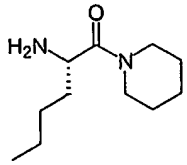
Table B

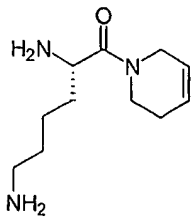
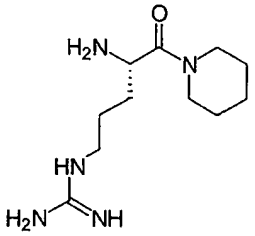
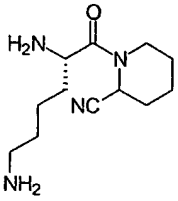
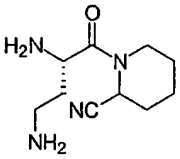
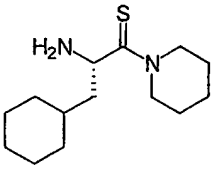
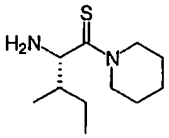
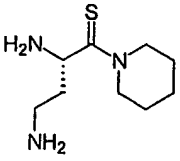
Formula	compound	IC_{50} DPPII (μM)	IC_{50} DPPIV (μM)
IV		0.00203	247

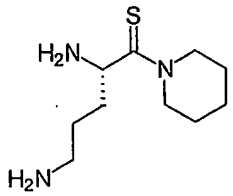
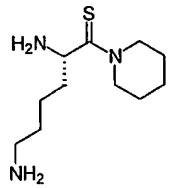
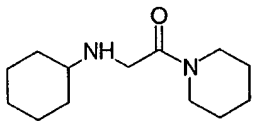
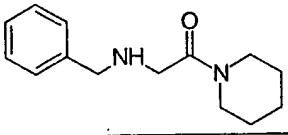
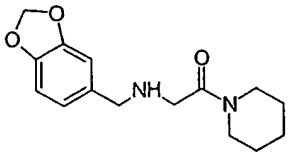
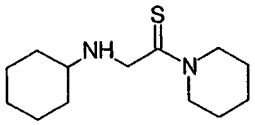
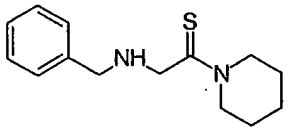
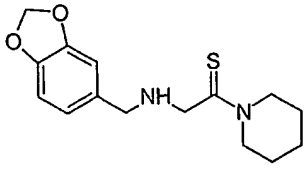
V		0.13	>1000
VI		130	>1000
VII		0.51	> 1000
VIII		29.3	> 1000
IX		190	> 1000
X		1.15	500
XI		12.5	> 1000

XII		1.5	518
XIII		0.085	64
XIV		20	> 1000
XV		1.8	545
XVI		7.4	> 1000
XVII		57.85	> 1000
XVIII		35.5	> 1000

XIX		537	> 1000
XX		3.1	> 1000
XXI		17	> 1000
XXII		1.6	247
XXIII		2.1	134.9
XXIV		0.45	> 500

XXV		1.84	> 1000
XXVI		0.33	213
XXVII		9.9	217
XXVIII		62	67
XXIX		21.7	> 1000
XXX		88.7	250
XXXI		57.1	229
XXXII		32.4	250

XXXIII		10.9	> 500
XXXIV		0.63	18.1
XXXV		1.48	51.2
XXXVI		0.046	151.9
XXXVII		8.0	1000
XXXVIII		16.7	23.9
XXXIX		0.22	> 1000

XXXX		0.2	> 1000
XXXXI		0.49	> 1000
XXXXII		138	> 1000
XXXXIII		not analysed	> 1000
XXXXIV		51.9	> 1000
XXXXV		69.1	> 1000
XXXXVI		48.3	> 1000
XXXXVII		42	> 1000

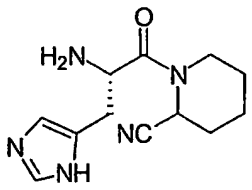
As illustrated in this example, the compounds according to the invention strongly inhibit DPPII activity, as indicated by the low IC_{50} values of the illustrated compounds for DPPII. In particular, most of the compounds in the following examples have an activity in inhibiting DPPII generally lower than 100 µM and in some cases lower than 10µM and even lower than 1 µM. Such results are indicative of the intrinsic activity of the compounds in use as inhibitors of DPPII enzyme activity.

In particular, the compound with formula IV is a particularly active and selective DPPII inhibitor. This compound has an IC_{50} value of 0.00203 µM for DPPII. For comparison, the IC_{50} value of this compound towards DPP IV comprises 247 µM. This compound thus has a particularly high selectivity of for DPPII, and is particularly suitable for in applications wherein a differentiation is required between DPP II and DPP IV activity.

In a preferred embodiment of the present invention, the present compounds may be active, i.e. have a strong inhibitory activity on DPP II. In addition, in another preferred embodiment, the present compounds as claimed in claim 1 may show a high selectivity for DPPII.

Due to their inhibiting activity, the presented compounds are very useful to be applied in all kinds of research, therapeutic and diagnostic applications for inhibiting the activity of a serine type dipeptidyl peptidase.

In another preferred embodiment a compound according to the invention is represented with following formula III:



Formula III

Example 3 Synthesis of the compounds according to the invention

The present example illustrates the synthesis of compounds as illustrated in Table B of example 2, according to different synthesis schemes.

The compounds having formulas IV, IX, XI, XII, XIII, XIV, XV, XVI and XXI as illustrated in example 2, Table B, are synthetised as follows. The synthesis of compounds having formulas IV, IX, XI, XII, XIII, XIV, XV, XVI and XXI is illustrated in Figure 1.

N^1-benzyl-4-oxo-4-(1-piperidinyl)-1,3(S)-butanediamine (IV)

Procedure A

To a mixture of *N*-α-benzyloxycarbonyl-*N*-ε-*tert*-butyloxycarbonyl-*L*-diaminobutyric acid (19.4 mmol), triethylamine (53.8 mmol) and TBTU (19.4 mmol) in DMF (40 ml) was added piperidine (17.6mmol). After stirring at room temperature overnight, water was added and the mixture was extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with 1N HCl (2 x 25 ml), 5% $NaHCO_3$ (2 x 25 ml) and brine (25 ml). The organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography (94%).

Procedure B

Deprotection of *tert*-butyloxycarbonyl (Boc) was done by dissolving in 15 ml of a TFA/dichloromethane (1:1) mixture. The solution was stirred for 3 h and the volatile part was removed under reduced pressure. After coevaporating several times with ether, the oily residue was used as such for the next step (95%).

Procedure C

To a mixture of compound obtained in previous step (2.3 mmol) and the appropiate aldehyde/keton (**IV**: benzaldehyde) (2.3 mmol) in dry methanol (15 ml) was added $NaCNBH_3$ (1.65 mmol). The mixture was stirred overnight at room temperature. Concentrated HCl was added until pH < 2, and the methanol was removed *in vacuo*. The residue was taken up in 20 ml of water and extracted with diethylether (2 x 20 ml). The aqueous solution was brought to pH > 11 with 2N NaOH and extracted several times with diethylether. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by preparative TLC using EtOAc/MeOH (95:5) as eluent (50%).

Procedure D

Deprotection of the benzyloxycarbonyl (Z) group was done by acidolysis: the compound resulted from previous step was dissolved in 30% HBr in acetic acid. After completion of the deprotection which was monitored by TLC, the volatile part was removed *in vacuo*. The residue was coevaporated several times with diethylether and was finally precipitated in diethylether (90%).

^{1}H-NMR (D_2O, 400 MHz) δ 1.58-1.74 (m, 6H, CH_2), 2.29-2.48 (m, 2H, β-CH_2), 3.15-3.24 (m, 2H, γ-CH_2), 3.48-3.60 (m, 4H, CH_2), 4.36 (s, 2H, CH_2), 4.65-4.74 (m, 1H, α-CH), 7.58 (s, 5H, H_{arom}); MS (ES^+) m/z 276 $(M + H)^+$; HPLC (214 nm): rt 9.92 min, 94%.

Benzyl 3-amino-1(S)-(1-piperidinylcarbonyl)propylcarbamate (IX)

The title compound was obtained according to procedure A, followed by procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.41-1.71 (m, 6H, CH_2), 1.98-2.17 (m, 2H, β-CH_2), 3.02-3.76 (m, 6H, γ-CH_2, CH_2), 4.70-4.85 (m, 1H, α-CH), 5.17 (s, 2H, CH_2), 7.46 (s, 5H, H_{arom}); MS (ES^+) m/z 320 $(M + H)^+$; LC-MS: rt 17.3 min, 100%, m/z 320 $(M + H)^+$; UV-HPLC: rt 14.48 min, 96%.

N^1-benzyl-2(S)-(1-piperidinylcarbonyl)-1,4-butanediamine (XI)

The synthesis of this compound started by carrying out procedure A.

Procedure E

Deprotection of the benzyloxycarbonyl (Z) group was done by hydrogenolysis: to a mixture of compound obtained from previous step in methanol (50 ml) was added Pd/C (20%) and acetic acid (1ml). A flow of nitrogen-gass was carried over the solution for 10 minutes, followed by a flow of H_2-gas. The reaction was monitored by TLC. After completion, again a flow of nitrogen was carried over the solution for 10 minutes. The mixture was filtered over a celite and the methanol was removed in vacuo. The compound obtained was used as such in the next step.

Reductive amination was carried out with benzaldehyde according to procedure C. The title compound was finally obtained by deprotection of the tert-butyloxycarbonyl group using procedure B. The final product could be precipitated in diethylether.

MS (ES^+) m/z 276 $(M + H)^+$; HPLC (214 nm): rt 10.63 min, 98%.

N-[3(S)-amino-4-oxo-4-(1-piperidinyl)butyl]acetamide (XII)

The synthesis of this compound started following procedure A and B.

Procedure F

The compound (1.57 mmol) obtained from previous step was dissolved in pyridine (5 ml) and acetic acid anhydride (2.35 mmol) was added. The solution was stirred overnight and pyridine was evaporated *in vacuo*. The residue was extracted with 2N HCl and diethylether. The combined organic layers were dried over Na_2SO_4 and evaporated. Purification was carried out by preparative TLC using EtOAc/MeOH (95:5) as eluent (50%).

The title compound was finally obtained by deprotection of the benzyloxycarbonyl group according to procedure D.

^{1}H-NMR (D_2O, 400 MHz) δ 1.55-1.76 (m, 6H, CH_2), 2.03-2.18 (m, 5H, CH_3, β-CH_2), 3.30-3.64 (m, 6H, γ-CH_2, CH_2), 4.41-4.67 (m, 1H, α-CH); MS (ES^+) m/z 228 $(M + H)^+$; HPLC (214 nm): rt 6.50 min, 96%.

4-Oxo-4-(1-piperidinyl)-N^1-(4-piperidinyl)-1,3(S)-butanediamine (XIII)

This compound was synthesised according to procedure A and B, followed by procedure C using benzyl 4-oxo-1-piperidinecarboxylate for reductive amination. The title compound was finally obtained by deprotection of the benzyloxycarbonyl group according to procedure D.

MS (ES^+) m/z 269 $(M + H)^+$; HPLC (214 nm): rt 5.46 min, 90%.

Benzyl-4-{[4-amino-2(S)-(1-piperidinylcarbonyl)butyl]amino}-1-piperidinecarboxylate (XIV)

This compound was synthesised according to procedure A and E, followed by procedure C using 4-oxo-Z-piperidine for reductive amination. The title compound was finally obtained by deprotection of the tert-butyloxycarbonyl group according to procedure B. The final product could be precipitated in diethylether.

MS (ES^+) m/z 403 $(M + H)^+$; HPLC (214 nm): rt 14.25 min, 96%.

N-[3(S)-amino-4-oxo-4-(1-piperidinyl)butyl]guanidine (XV)

The synthesis of this compound started according to procedure A and B.

Procedure G

To a stirred solution of 1-H-pyrazole-1-[*N*, *N*'-bis(tert-butyloxycarbonyl)]carboxamide (1.2 mmol) in ACN/H_2O (95:5, 20 ml) was added the appropiate amine (1.2 mmol) and DIEA (3.6 mmol). The mixture was refluxed for 2h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by preparative TLC using DCM/MeOH (95:5) as eluent.

Deprotection of the tert-butyloxycarbonyl groups was done according to procedure B. Finally the title compound was obtained by deprotection of the benzyloxycarbonyl group according to procedure E.

MS (ES^+) m/z 228 $(M + H)^+$; HPLC (214 nm): rt 5.61 min, 95%.

N-[3-amino-1(S)-(1-piperidinylcarbonyl)propyl]guanidine (XVI)

This compound was synthesised according to procedure A and E, followed by procedure G. The title compound was finally obtained by deprotection of the tert-butyloxycarbonyl groups according to procedure B. The final product could be precipitated in diethylether.

MS (ES^+) m/z 228 $(M + H)^+$.

4-oxo-4-(1-piperidinyl)-N^3-(4-piperidinyl)-1,3(S)-butanediamine (XXI)

This compound was synthesised according to procedure A and E, followed by procedure C benzyl 4-oxo-1-piperidinecarboxylate for reductive amination. The title compound was finally obtained by deprotection of the tert-butyloxycarbonyl group and benzyloxycarbonyl group according to procedure D. The final product could be precipitated in diethylether.

MS (ES^+) m/z 269 $(M + H)^+$.

The compounds having formulas XVIII, XVII and XX as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds illustrated in Figure 2.

Benzyl 4{[2-oxo-2-(1-piperidinyl)ethyl]amino}-1-piperidinecarboxylate (XVIII)

The synthesis of this compound started from N-α-tert.-butyloxycarbonyl-L-glycine and was carried out according to procedure A, followed by procedure B. Reductive amination with benzyl 4-oxo-1-piperidinecarboxylate was done using procedure C to obtain the title compound.

MS (ES^+) m/z 360 $(M + H)^+$; HPLC (214 nm): rt 16.03 min, 92%.

N-(2-oxo-2-piperidin-1-ylethyl)piperidin-4-amine (XVII)

The synthesis of this compound started from compound **XVIII**. The title compound was obtained by deprotection of the benzyloxycarbonyl group according to procedure D.

^{1}H-NMR (D_2O, 400 MHz) δ 1.51-1.68 (m, 6H, CH_2), 1.89-1.99 (m, 2H, CH_2), 2.39-2.43 (m, 2H, CH_2), 3.10-3.16 (m, 2H, CH_2), 3.35-3.38 (m, 2H, CH_2), 3.49-3.51 (m, 2H, CH_2), 3.57-3.62 (m, 3H, CH, CH_2), 4.21 (s, 2H, CH_2); MS (ES^+) m/z 226 $(M + H)^+$; HPLC (214 nm): rt 6.21 min, 94%.

1-Benzyl-N-[2-oxo-2-(1-piperidinyl)ethyl]-4-piperidinamine (XX)

The synthesis of this compound started from compound **XVIII**.

Procedure H

To a solution of compound **XVIII** (5.7 mmol) in dioxane/H_2O (1:1, 20 ml) was added TEA (17.2 mmol) and Boc_2O (6.3 mmol). The mixture was stirred at room temperature for 5 hours. The dioxane was evaporated under reduced pressure, the aqueous solution was acidified and extracted with EtOAc (2 x 50 ml). The combined organic layers were dried over Na_2SO_4 and evaporated.

Deprotection of the benzyloxycarbonylgroup was done according to procedure E, followed by reductive amination with benzylaldehyde according to procedure C. The title compound was obtained by final deprotection of the *tert*-butyloxycarbonyl group using procedure B. The final product could be precipitated in diethylether.

MS (ES^+) m/z 316 $(M + H)^+$.

The compounds having formulas V, VI, VII, VIII, X and XIX as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds is illustrated in Figure 3.

4-Oxo-4-(1-piperidinyl)-1,3(S)-butanediamine (V)

The synthesis of this compound started from *N*-α,γ-di-*tert.*-butyloxycarbonyl-*L*-diaminobutyric acid.

Procedure I

Compounds were prepared by parallel synthesis using a PASP-protocol: protected amino acid (0.375 mmol), HOBt (0.425 mmol) and PS-Carbodiimide (0.75 mmol) were added to a dry reaction vessel. Dichloromethane (4 ml) was added and the mixture was stirred for 10 min prior to the addition of the appropriate amine. After stirring at room temperature overnight the polymer-bound polyamine (1.5 mmol) was added and stirring was continued for 5 h. The reaction mixture was filtered and the amide product was collected in the filtrate. The resins are washed two times with 4 ml of dichloromethane and the combined fractions were evaporated under reduced pressure. The purity of the compounds was checked by TLC and reverse phase HPLC. Compounds were purified by preparative TLC using a mixture of EtOAc and hexane (usually 40/60) as eluent.

The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.73 (m, 6H, CH_2), 2.27-2.34 (m, 2H, β-CH_2), 3.12-3.23 (m, 2H, γ-CH_2), 3.50-3.71 (m, 4H, CH_2), 4.72 (t, 1H, α-CH); LC-MS: rt 0.8 min, 100%, m/z 186 $(M + H)^+$; HPLC (214 nm): rt 3.62 min, 100%.

4-Oxo-4-(1-piperidinyl)-1,3(R)-butanediamine (VI)

The synthesis of this compound started from *N*-α,γ-di-*tert.*-butyloxycarbonyl-*D*-diaminobutyric acid according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.62 (m, 6H, CH_2), 2.15-2.21 (m, 2H, β-CH_2), 3.02-3.11 (m, 2H, γ-CH_2), 3.41-3.59 (m, 4H, CH_2), 4.61 (t, 1H, α-CH); LC-MS: rt 0.7 min, 100%, m/z 186 (M + H)$^+$; HPLC (214 nm): rt 4.66 min, 100%.

4-(4-morpholinyl)-4-oxo-1,3(*S*)-butanediamine (VII)

The synthesis of this compound started from *N*-α,γ-di-*tert.*-butyloxycarbonyl-*L*-diaminobutyric acid according to procedure I using morfoline as amine compound. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 2.27-2.38 (m, 2H, β-CH_2), 3.12-3.28 (m, 2H, γ-CH_2), 3.61-3.85 (m, 8H, CH_2), 4.71 (t, 1H, α-CH); LC-MS: rt 0.6 min, 100%, m/z 188 (M + H)$^+$; HPLC (214 nm): rt 3.41 min, 100%.

4-oxo-4-(1-piperazinyl)-1,3(*S*)-butanediamine (VIII)

The synthesis of this compound started from *N*-α,γ-di-*tert.*-butyloxycarbonyl-*L*-diaminobutyric acid according to procedure I using Boc-piperazine as amine compound. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 2.25-2.40 (m, 2H, β-CH_2), 3.12-3.28 (m, 2H, γ-CH_2), 3.33-3.50 (m, 4H, CH_2),), 3.75-4.15 (m, 4H, CH_2) 4.76 (t, 1H, α-CH); LC-MS: rt 0.5 min, 94%, m/z 187 (M + H)$^+$; HPLC (214 nm): rt 3.40 min, 100%.

Benzyl 3-amino-4-oxo-4-(1piperidinyl)butylcarbamate (X)

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*N*-γ-benzyloxycarbonyl-*L*- diaminobutyric acid according to procedure I using piperidine as amine compound. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.20-1.71 (m, 6H, CH_2), 1.85-2.05 (m, 2H, β-CH_2), 3.29-3.55 (m, 6H, CH2, γ-CH_2), 4.44 (m, 1H, α-CH), 5.13 (s, 2H, CH_2), 7.43 (s, 5H, H_{arom}); LC-MS: rt 17.2 min, 99%, m/z 320 (M + H)$^+$; UV-HPLC: rt 14.85 min, 97%.

***N*-[2-oxo-2-(1-piperidinyl)ethyl]cyclopentanamine (XIX)**

Procedure J

To a stirred and cooled solution of the appropiate amine (50 mmol) in diethylether (10 ml) was added dropwise over 30 minutes a solution of bromoacetic acid (10 mmol) in diethylether (2 ml). The mixture was stirred several hours at 0 °C and was then allowed to warm up and stirred overnight. The pH was raised to 12 with 2N NaOH and extracted with ether to remove unreacted amine. The aqueous layer was acidified (pH = 1) and evaporated in vacuo. The residue was taken up in a small volume of methanol, filtrated and evaporated under reduced pressure. The residue was used as such in the next step. Introduction of tert-butyloxycarbonyl (Boc) was done according to

procedure H. The title compound was finally obtained according to procedure I using piperidine as amine compound, followed by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.49-1.72 (m, 12H, CH_2) , 2.02-2.07 (m, 2H, CH_2), 3.31 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 3.51-3.59 (m, 1H, CH), 4.03 s, 2H, CH_2); MS (ES^+) m/z 211 $(M + H)^+$; HPLC (214 nm): rt 9.52, 98%.

The compounds having formulas XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, XXXIV as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds is illustrated in Figure 4.

6-oxo-6-(1-piperidinyl)-1,5(*S*)-hexanediamine (XXII).

The synthesis of this compound started from *N*-α,ε-di-*tert*.-butyloxycarbonyl-*L*-lysine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.34-1.87 (m, 12H, CH_2), 2.95 (t, 2H, ε-CH_2), 3.43-3.53 (m, 4H, CH_2), 4.50 (t, 1H, α-CH); LC-MS rt 1.0 min, 93%, m/z 214 $(M + H)^+$; HPLC (214 nm): rt 2.59 min, 86%.

benzyl 5(*S*)-amino-6-oxo-6-(1-piperidinyl)hexylcarbamate (XXIII).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*N*-ε-benzyloxycarbonyl-*L*-lysine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.37-1.76 (m, 10H, CH_2), 1.84-1.98 (m, 2H, CH_2), 3.14-3.28 (m, 2H, ε-CH_2), 3.41-3.68 (m, 4H, CH_2), 4.47-4.57 (m, 1H, α-CH), 5.11-5.26 (m, 2H, CH_2-Z), 7.49 (s, 5H, H_{arom}); LC-MS rt 18.7 min, 100%, m/z 348 $(M + H)^+$; HPLC (214 nm): rt 14.59 min, 100%.

5-oxo-5-(1-piperidinyl)-1,4(*S*)-pentanediamine (XXIV).

The synthesis of this compound started from *N*-α-benzyloxycarbonyl-*N*-δ-*tert.*-butyloxycarbonyl-*L*-ornithine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure D.

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.91 (m, 8H, CH_2), 1.97-2.03 (m, 2H, CH_2), 3.11 (t, 2H, δ-CH_2), 3.53-3.66 (m, 4H, CH_2), 4.66 (t, 1H, α-CH); LC-MS rt 0.8 min, 100%, m/z 200 $(M + H)^+$; HPLC (214 nm): rt 3.74 min, 100%.

3-oxo-3-(1-piperidinyl)-1,2(*S*)-propanediamine (XXV).

The synthesis of this compound started from *N*-α,β-di-*tert.*-butyloxycarbonyl-*L*-2,3-diaminopropanoic acid according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.57-1.81 (m, 6H, CH_2), 3.42-3.85 (m, 6H, CH_2, β-CH_2), 4.97 (m, 1H, α-CH); LC-MS rt 0.7 min, 100%, m/z 172 $(M + H)^+$; HPLC (214 nm): rt 3.60 min, 100%.

3-(1*H*-imidazol-4-yl)-1-oxo-1-(1-piperidinyl)-2(*S*)-propanamine (XXVI).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*N*-im-trityl-*L*-histidine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.52-1.79 (m, 6H, 3-CH_2, 4-CH_2, 5-CH_2), 3.31-3.72 (m, 6H, β-CH_2, 2-CH_2, 6-CH_2), 4.81-4.93 (m, 1H, α-CH), 7.54 (s, 1H, 4-CH-His), 8.81 (s, 1H, 2-CH-His); LC-MS rt 1.0 min, 100%, m/z 223 $(M + H)^+$; HPLC (214 nm): rt 4.04 min, 88%.

3-cyclohexyl-1-oxo-1-(1-piperidinyl)-2(*S*)-propanamine (XXVII)

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*L*-cyclohexylalanine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 0.91-1.79 (m, 19H, CH_2), 3.40-3.53 (m, 4H, 2-CH_2, 6-CH_2), 4.49 (t, 1H, α-CH); MS (ES^+) m/z 239 $(M + H)^+$; LC-MS rt 1.0-1.4 min, m/z 239 $(M + H)^+$; UV-HPLC rt 23.49 min, 100%.

3-methyl-1-oxo-1-(1-piperidinyl)-2(*S*)-pentanamine (XXVIII).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*L*-isoleucine acid according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ 0.85 (t, 3H, δ-CH_3), 0.94 (d, 3H, γ-CH_3), 1.00-1.25 (m, 1H, γ-CH), 1.35-1.70 (m, 7H, γ-CH, 3-CH_2, 4-CH_2, 5-CH_2), 1.70-1.85 (m, 1H, β-CH), 3.20-3.65 (m, 4H, 2-CH_2, 6-CH_2), 4.25 (d, 1H, α-CH), 8.07 (br s, 3 H, NH_3+); MS (ES^+) m/z 199 $(M + H)^+$; LC-MS rt 0.6-0.7 min, m/z 199 $(M + H)^+$; UV-HPLC rt 11.30 min, 100%.

2(*S*)-amino-3-oxo-3-(1-piperidinyl)-1-propanol (XXIX).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*O*-*tert.*-butyl-*L*-serine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.73 (m, 6H, CH_2), 3.50-3.64 (m, 4H, CH_2), 3.90-3.95 (m, 1H, β-CH_2), 4.02-4.06 (m, 1H, β-CH_2), 4.62-4.68 (m, 1H, α-CH); MS (ES^+) m/z 173 $(M + H)^+$; LC-MS rt 0.5-0.6 min, m/z 173 $(M + H)^+$; UV-HPLC rt 4.91 min, 93%.

1-oxo-1-(1-piperidinyl)-2(*S*)-butanamine (XXX).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*L*-2-aminobutyric acid according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.05 (t, 3H, CH_3), 1.63-1.77 (m, 6H, CH_2), 1.89-2.00 (m, 2H, β-CH_2), 3.50-3.68 (m, 4H, CH_2), 4.52 (t, 1H, α-CH); MS (ES^+) m/z 171 $(M + H)^+$; LC-MS rt 0.5-0.6 min, m/z 171 $(M + H)^+$; UV-HPLC rt 7.92 min, 96%.

1-oxo-1-(1-piperidinyl)-2(*S*)-pentanamine (XXXI).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*L*-norvaline according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.01 (t, 3H, CH_3), 1.41-1.51 (m, 2H, γ-CH_2), 1.59-1.78 (m, 6H, CH_2), 1.85-1.89 (m, 2H, β-CH_2), 3.50-3.68 (m, 4H, CH_2), 4.55 (t, 1H, α-CH); MS (ES^+) m/z 185 $(M + H)^+$; LC-MS rt 0.7-0.8 min, m/z 185 $(M + H)^+$; UV-HPLC rt 9.91 min, 100%.

1-oxo-1-(1-piperidinyl)-2(*S*)-hexanamine (XXXII).

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*L*-norleucine according to procedure I. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 0.95 (t, 3H, CH_3), 1.30-1.42 (m, 4H, CH_2), 1.59-1.76 (m, 6H, CH_2), 1.87-1.90 (m, 2H, β-CH_2), 3.49-3.69 (m, 4H, CH_2), 4.54 (t, 1H, α-CH); MS (ES^+) m/z 199 $(M + H)^+$; LC-MS rt 0.5-0.7 min, m/z 199 $(M + H)^+$; UV-HPLC rt 11.96 min, 96%.

6-(3,6-dihydro-1(2*H*)-pyridinyl)-6-oxo-1,5(*S*)-hexanediamine (XXXIII).

The synthesis of this compound started from *N*-α,ε-di-*tert.*-butyloxycarbonyl-*L*-lysine according to procedure I using 1,2,3,6-tetrahydropyridine as amine compound. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.45-1.55 (m, 2H, CH_2), 1.69-1.81 (m, 2H, CH_2), 1.91-2.00 (m, 2H, CH_2), 2.23-2.36 (m, 2H, 5-CH_2), 3.05 (b, 2H, ε-CH_2), 3.62-3.81 (m, 2H, 6-CH_2), 4.03-4.17 (m, 2H, 2-CH_2), 4.55 (t, 0.5H, α-CH), 4.62 (t, 0.5H, α-CH), 5.75-5.82 (m, 1H, 4-CH), 5.96-6.06 (m, 1H, 3-CH); MS (ES^+) m/z 212 $(M + H)^+$.

***N*-[4(*S*)-amino-5-oxo-5-(1-piperidinyl)pentyl]guanidine (XXXIV).**

The synthesis of this compound started from *N*-α-*tert.*-butyloxycarbonyl-*Nγ*,*Nγ*-bis-benzyloxycarbonyl-*L*-arginine according to procedure I. Deprotection of the benzyloxycarbonyl groups was done according to procedure E. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.80 (m, 8H, CH_2), 1.92-2.00 (m, 2H, CH_2), 3.25-3.38 (m, 2H, δ-CH_2), 3.44-3.77 (m, 4H, CH_2), 4.60-4.70 (m, 1H, α-CH); LC-MS rt 1.0 min, 98%, m/z 242 $(M + H)^+$; HPLC (214 nm): rt 4.58 min, 91%.

The compounds having formulas XXXV and XXXVI as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds is illustrated in Figure 5.

1-(*S*-2,6-Diaminohexanoyl)-2(*R,S*)-piperidinecarbonitrile (XXXV).

Procedure K

L-HomoProNH$_2$ was prepared from *L*-pipecolinic acid (1 eq) by reaction with *N*-hydroxysuccinimide (1.05 eq) and dicyclohexylcarbodiimide (DCC, 1.05 eq) in DCM (yield: 90%), followed by treatment of a solution of the obtained compound in dioxane with ammonium gas (yield: 99%).

The synthesis of the title compound started by coupling *N*-α,γ–di-*tert.*-butyloxycarbonyl-*L*-lysine 2-*D,L*-piperidinecarboxamide according to procedure A.

Procedure L

Dehydratation of the amide function to the nitrile was done according the following procedure: To a solution of Boc-Xaa-YaaNH$_2$ (1 eq) and imidazol (2 eq) in pyridine at –30 °C was slowly added phosphorusoxychloride (4 eq). The solution was allowed to attain room temperature and the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated and the residue was extracted with 1N HCl and diethylether. The organic layer was dried, evaporated and the residue was purified by prepartive TLC to yield the Boc protected dipeptide nitrile (60%).

The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl groups according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.42-1.63 (m, 3H, CH_2), 1.71-2.02 (m, 8H, CH_2), 2.18-2.29 (m, 1H, CH_2), 3.00-3.41 (m, 2H, 6-CH_2), 3.46-3.50 (m, 1H, ε-CH_2), 3.88-4.00 (m, 1H, ε-CH_2), 4.53-4.67 (m, 1H, α-CH), 5.69-5.88 (m, 1H, 2-CH); LC-MS rt 1.0 min, 100%, m/z 239 $(M + H)^+$; HPLC (214 nm): rt 5.78 min, 99%.

1-(*S*-2,4-diaminobutanoyl)-2(*S*)-piperidinecarbonitrile (XXXVI).

The synthesis of the title compound started by coupling *N*-α, γ-di-*tert.*-butyloxycarbonyl-*L*-diaminobutyric acid and 2-*L*-piperidinecarboxamide according to procedure A. Dehydratation of the amide function to the nitrile was done according to procedure L. Finally, the title compound was obtained by deprotection of the *tert*-butyloxycarbonyl groups according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.68 (m, 1H, CH_2), 1.72-2.00 (m, 4H, CH_2), 2.08-2.19 (m, 1H, CH_2), 2.35-2.49 (m, 2H, CH_2), 3.10-3.29 (m, 2H, 6-CH_2), 3.48-3.53 (m, 1H, γ-CH_2), 3.85-3.98 (m, 1H, γ-CH_2), 4.70-4.82 (m, 1H, α-CH), 5.69-5.89 (m, 1H, 2-CH_2); LC-MS rt 0.8 min, 100%, m/z 211 $(M + H)^+$; HPLC (214 nm): rt 6.56 min, 100%.

The compounds having formulas XXXVII to XXXXI as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds is illustrated in Figure 6.

3-cyclohexyl-1-(1-piperidinyl)-1-thioxo-2(*S*)-propanamine (XXXVII)

procedure M

The protected amino acids amides were procuced according to procedure I. To a solution of these compounds (2 eq) in 5 ml of toluene was added 2,4-bis(*p*-methoxyphenyl)-1,3-dithiadiphosphatane 2,4-disulfide (Lawesson's reagent) (1 eq). The reaction mixture was stirred for 2 h at 80°C. The solvent was removed by evaporation and the crude compound was purified by preparative TLC (EtOAc/hexane, 40:60).

Finally, the title compound was obtained by deprotection of the *tert*-butyloxycarbonyl groups according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 0.95-2.1 (m, 19H, CH_2, CH), 3.71-3.90 (m, 2H, CH_2), 4.15-4.39 (m, 2H, CH_2), 4.62-4.75 (m, 1H, α-CH); MS (ES^+) m/z 255 $(M + H)^+$.

2-(*S*)-methyl-1-(1-piperidinylcarbothioyl)butylamine (XXXVIII)

The synthesis of this compound was started according to procedure M. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 0.95-1.08 (m, 6H, CH_3), 1.10-2.12 (m, 9H, CH_2, CH), 3.10-3.26 (m, 1H, CH_2), 3.71-3.95 (m, 2H, CH_2), 4.1-4.21 (m, 1H, CH_2), 4.42-4.50 (m, 0.5H, α-CH),4.6-4.76 (m, 0.5H, α-CH); MS (ES^+) m/z 215 $(M + H)^+$.

4-(1-piperidinyl)-4-thioxo-1,3(*S*)-butanediamine (XXXIX)

The synthesis of this compound was started according to procedure M. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B.

^{1}H-NMR (D_2O, 400 MHz) δ 1.61- 1.63 (m, 6H, 3-CH_2, 4-CH_2, 5-CH_2), 2.30-2.35 (m, 2H, β-CH_2), 3.10-3.26 (m, 2H, γ-CH_2), 3.82-3.98 (m, 2H) and 4.12-4.20 (m, 1H) and 4.36-4.44 (m, 1H) (2-CH_2, 6-CH_2), 4.91 (t, 1H, α-CH); MS (ES^+) m/z 202 $(M + H)^+$.

5-(1-piperidinyl)-5-thioxo-1,4(*S*)-pentanediamine (XXXX)

The synthesis of this compound was started according to procedure M. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B. ^{1}H-NMR (D_2O, 400 MHz) δ 1.82-1.99 (m, 8H, CH_2), 2.03-2.09 (m, 2H, β-CH_2), 3.12 (t, 2H, δ-CH_2), 3.89-4.03 (m, 2H, CH_2), 4.20-4.27 (m, 1H, CH_2), 4.42-4.48 (m, 1H, CH_2), 4.90 (t, 1H, α-CH); MS (ES^+) m/z 216 $(M + H)^+$.

6-(1-piperidinyl)-6-thioxo-1,5(*S*)-hexanediamine (XXXXI)

The synthesis of this compound was started according to procedure M. The title compound was obtained by deprotection of the *tert*-butyloxycarbonyl group according to procedure B. ^{1}H-NMR (D_2O, 400 MHz) δ 1.43-1.62 (m, 2H) and 1.71-1.83 (m, 8H) (γ-CH_2, δ-CH_2, 3-CH_2, 4-CH_2, 5-CH_2), 1.93-2.00 (m, 2H, β-CH_2), 3.04 (t, 2H, ε-CH_2), 3.80-3.96 (m, 2H) and 4.07-4.22 (m, 1H), 4.34-4.41 (m, 1H) (2-CH_2, 6-CH_2), 4.74- 4.79 (m, 1H, α-CH); MS (ES^+) m/z 230 $(M + H)^+$.

The compounds having formulas XXXXII to XXXXVII as illustrated in example 2, Table B, are synthetised as follows. The synthesis of these compounds is illustrated in Figure 7.

***N*-cyclohexyl-2-oxo-2-(1-piperidinyl)-ethaneamine (XXXXII)**

Cyclohexylamine was protected with a *tert*-butyloxycarbonyl(Boc)-group carrying out procedure **H**.

Procedure N.

For the synthesis of *N*-Boc-*N*-cyclohexylglycine ethyl ester, *N*-Boc-Cyclohehexylamine (10 mmol) dissolved in freshly dried THF (50ml) was cooled to –78°C under nitrogen. To this solution was dropped *n*-BuLi (11mmol) over a period of 2 minutes. After Stirring for 5 minutes, ethyl bromoacetate (11mmol), dissolved in dry ether (5ml) was added in one portion *via* a syringe and the cooling bath was removed. The solution was allowed to reach room temperature and stirred for another 2 hours. Then, all volatile components were evaporated. In this way, the crude product was obtained.

Procedure O

For the synthesis of *N*-Boc-*N*-cyclohexylglycine, the crude product obtained by carrying out procedure N., was mixed with a 1M solution of KOH in aqueous 70% MeOH (12ml). After

stirring for 4 hours at rt, the solvent was evaporated under reduced pressure and the residue redissolved in water (140 ml). The aqueous layer was washed with diethylether (2x50 ml), acidified to pH=1 and extracted with EtOAc (2x50ml). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure yielding *N*-Boc-*N*-cyclohexylglycine, which was recrystallised from EtOAc/Hexanes (1:4). (72% over three steps).

The *N*-Boc protected title compound was obtained by submitting *N*-Boc-*N*-cyclohexylglycine to procedure **A** (81%)

The title compound was obtained by deprotection with a TFA/DCM mixture (1:1) acoording to procedure **B** and precipitation from dry ether.(84%).

^{1}H-NMR (D_2O, 400MHz) δ1.15-1.31(m, 2H, CH_2(Cy)) 1.34-1.49(m, 4H, CH_2(Cy)) 1.51-1.78(m, 6H, CH_2) 1.81-1.98(m, 2H, CH_2(Cy)) 2.01-2.11(m, 1H, CH_2(Cy)) 2.13-2.25(m, 1H, CH_2(Cy)) 3.01-3.21(m, 1H, CH(Cy)) 3.38-3.47(m, 2H, CH_2) 3.52-3.68(m, 2H, CH_2) 4.06-4.11(s, 2H, CH_2)

MS(ES$^+$): m/z 225.3 $(M+H)^+$

_N_-benzyl-2-oxo-2-(1-piperidinyl)-ethaneamine (XXXXIII)

The title compound was obtained by sequentially applying procedures **H**, **N**, **O**, **A** and B to benzylamine.

^{1}H-NMR (D_2O, 400MHz) δ1.43-1.52(m, 4H, CH_2) 1.54-1.68(m, 2H, CH_2) 3.24-3.33(m, 2H, CH_2) 3.37-3.53(m, 2H, CH_2) 3.97-4.09(s, 2H, CH_2) 4.21-4.33(s, 2H, $ArCH_2$) 7.38-7.59(br s, 5H, Ar).

MS(ES$^+$): m/z 233.1 $(M+H)^+$ m/z 255.2 $(m+Na)^+$

_N_-piperonyl-2-oxo-2-(1-piperidinyl)-ethaneamine (XXXXIV)

The title compound was obtained by sequentially applying procedures **H**, **N**, **O**, **A** and **B** to piperonylamine.

^{1}H-NMR (D_2O, 400MHz) δ1.46-1.55(m, 4H, CH_2) 1.58-1.69(m, 2H, CH_2) 3.18-3.27(m, 2H, CH_2) 3.33-3.46(m, 2H, CH_2) 3.74-3.92(s, 2H, $ArCH_2$) 3.99-4.12(s, 2H, CH_2) 4.21-4.33(s, 2H, $ArCH_2$) 6.51-6.82 (m, 1H, Ar) 6.86-7.14(br m, 2H, Ar).

MS(ES$^+$): m/z 277.2 $(M+H)^+$ m/z 289.3 $(M+Na)^+$

_N_-cyclohexyl-2-thioxo-2-(1-piperidinyl)-ethaneamine (XXXXV)

The title compound was obtained by sequentially applying procedures **M** and **B** to *N*-Boc- *N*-cyclohexyl-2-oxo-2-(1-piperidinyl)-ethaneamine.

^{1}H-NMR (D_2O, 400MHz) δ1.15-1.31(m, 2H, CH_2(Cy)) 1.34-1.49(m, 4H, CH_2(Cy)) 1.58-1.73(m, 6H, CH_2) 1.83-1.98(m, 2H, CH_2(Cy)) 2.0-2.12(m, 1H, CH_2(Cy)) 2.12-2.23(m, 1H, CH_2(Cy)) 2.98-3.17(m, 1H, CH(Cy)) 3.42-3.51(m, 2H, CH_2) 3.62-3.73(m, 2H, CH_2) 4.34-4.42(s, 2H, CH_2)

MS(ES$^+$): m/z 241.$(M+H)^+$

N-benzyl-2-thioxo-2-(1-piperidinyl)-ethaneamine (XXXXVI)

The title compound was obtained by sequentially applying procedures **M** and **B** to *N*-Boc- *N*-benzyl-2-oxo-2-(1-piperidinyl)-ethaneamine.

^{1}H-NMR (D_2O, 400MHz) δ1.46-1.55(m, 4H, CH_2) 1.54-1.68(m, 2H, CH_2) 3.28-3.36(m, 2H, CH_2) 3.39-3.51(m, 2H, CH_2) 4.14-4.28(s, 2H, CH_2) 4.24-4.37(s, 2H, $ArCH_2$) 7.38-7.59(br s, 5H, Ar).

MS(ES$^+$): m/z 249.3 $(M+H)^+$; m/z 271.2 $(M+Na)^+$

N-piperonyl-2-thioxo-2-(1-piperidinyl)-ethaneamine (XXXXVII)

The title compound was obtained by sequentially applying procedures M and B to *N*-Boc- *N*-piperonyl-2-oxo-2-(1-piperidinyl)-ethaneamine.

^{1}H-NMR (D_2O, 400MHz) δ1.44-1.569(br m, 6H, CH_2) 3.17-3.27(m, 2H, CH_2) 3.32-3.41(m, 2H, CH_2) 3.76-3.90(s, 2H, $ArCH_2$) 4.26-4.34(s, 2H, CH_2) 4.20-4.33(s, 2H, $ArCH_2$) 6.52-6.80 (m, 1H, Ar) 6.86-7.14(br m, 2H, Ar).

MS(ES$^+$):m/z 293.4$(M+H)^+$

Example 4 Use of a compound of the invention as affinity ligand during the purification of DPPII

This example illustrates the use of a compound (formula XXII) according to the present invention as affinity ligand during the purification of DPPII.

NHS-activated Sepharose 4 fast flow gel (Amersham) was used as matrix. An appropriate amount of the gel was washed on a sintered glass filter with 1 mM HCl. An excess of Lys-Pip (formula XXII) was solubilized in isopropanol (1 column volume) and allowed to react with the matrix during 24 h at room temperature in an end over end mixer. Afterwards the gel was washed with an excess isopropanol, followed by water. Remaining active groups were

blocked with 2 column volumes of 200 mM Tris-HCl pH 8.0 during 2 hours at room temperature. The additional washing procedure included 3 cycles of alternating pH wash steps. The low pH buffer consisted of 100 mM acetate pH 4.0 containing 500 mM NaCl. The high pH buffer consisted of 50 mM Tris base with 500 mM NaCl. The Lys-Pip affinity matrix was stored in 100 mM cacodylate at 4-8°C.

A biological sample containing DPPII was applied onto the Lys-Pip affinity matrix in Na-acetate buffer, 50 mM pH 5.5. Unbound protein was removed by washing with 100 mM cacodylate pH 5.5. Elution was performed with 100 mM cacodylate pH 5.5 containing 500 mM NaCl.

Example 5

The present example is a further illustration of the present invention.

In a further aspect, the invention relates to the development of highly specific and potent inhibitors of DPP II, which will contribute to the unravelling of the physiological functions of this enzyme and will be helpfull to differentiate between DPP II and DPP IV in biological systems. The resembling substrate specificity and catalytic mechanism can complicate this challenging task.

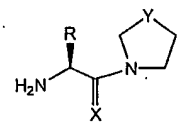
Dipeptidyl peptidases (DPPs, EC 3.4.14.-) have been identified in various mammalian tissues and catalyze the sequential release of dipeptides from polypeptides. Among these enzymes, DPP II (EC 3.4.14.2) and DPP IV (EC 3.4.14.5) preferentially release N-terminal dipeptide moieties (Xaa-Pro- or Xaa-Ala-) at acidic (DPP II) or weak basic (DPP IV) pH from some oligopeptides or proteins. Although DPP IV and DPP II share substrate specificity, they can be functionally and biochemically distinguished.

DPP II, first identified by McDonald at al. (J. Biol. Chem. 1968, 243, 4143-4150), is believed to be involved in the physiological breakdown of some proline-containing neuropeptides and in the degradation of collagen (Andersen, et al. Renal Physiol. Biochem, 1989, 12, 32-40) together with tripeptidyl peptidase. However, its physiological functions remain elusive and potential therapeutic targets of DPP II inhibitors are still unclear. DPP II is generally localized in lysosomes and is found in a number of mammalian tissues and body fluids. Recently it is reported to be identical to human quiescent cell proline dipeptidase (QPP), based on the

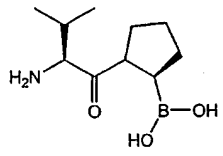
significant sequence homology (79.4%) found between human QPP and rat DPP II (Araki et al. J. Biochem., 2001, 129, 279-288). Human QPP, which was recently isolated and cloned from human T cells (Chiravuri et al. J. Immunol. 1999, 163, 3092-3099; Underwood et al. J. Biol. Chem. 1999, 274, 48, 34053-34058), is a 58-kDa glycoprotein functionally active as a homodimer formed with a leucine zipper motif (Chiravuri et al. J. Biol. Chem. 2000, 275, 35, 26994-26999). It has been shown that QPP inhibitors cause apoptosis in quiescent lymphocytes, but not in activated or transformed lymphocytes. This process is believed to be independent of DPP IV, because both DPP IV^+ and DPP IV^- T cells undergo apoptosis (Chiravuri et al. J. Immunol. 1999, 163, 3092-3099). No sequence homology has been found between DPP II/QPP and DPP IV.

DPP IV has been studied extensively over the last three decades and a broad array of diverse functional properties in the immune, nerve and endocrine system is suggested Augustyns et al. Curr. Med. Chem., 1999, 6, 311-327; Villhaueret al. Annual Reports in Medicinal Chemistry, Academic Press, 2001, Vol 36, pp 191-200). DPP IV is bound to the cell membrane and expressed quite ubiquitously in mammalian tissues. In the hematopoietic system it was identified as the leukocyte antigen CD26. Inhibition of DPP IV can be valuable in the treatment of type 2 diabetes and some important DPP IV inhibitors are currently under evaluation in this field (Villhaueret al. Annual Reports in Medicinal Chemistry, Academic Press, 2001, Vol 36, pp 191-200; Villhauer et al. J. Med. Chem. Lett., 2002). DPP IV inhibitors resemble often the dipeptide cleavage product with a proline mimic at the P_1-site. Amino acyl pyrrolidides (1) and thiazolidides (2) are known as potent, competitive inhibitors of DPP IV (see below). Substituting the pyrrolidine ring with 6- or 7-membered rings or acyclic amines results in loss of potency (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309). Substitution with a nitrile group in 1 or 2 at position 2 and 4 also affords competitive inhibitors with approximately a 1000-fold increase in potency compared to the parent compounds (Ashworth et al. Bioorg. Med. Chem. Lett., 1996, 6, 10, 1163-1166; ([1]) Li et al. Arch. Biochem. Biophys., 1995, 323, 1, 148-154; Ashworth et al. Bioorg. Med. Chem. Lett., 1996, 6, 22, 2745-2748). Introduction of a thio-amide bond, as a peptide bond surrogate, results in thioxo amino acid pyrrolidides (3) and thiazolidides (4), which are also reported to inhibit DPP IV as well as DPP II Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31). The inhibitory potential of all these compounds for DPP IV is well described and recently reviewed (Villhaueret al. Annual Reports in Medicinal Chemistry, Academic Press, 2001, Vol 36, pp

191-200; Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309). Hereunder Reported DPP II and DPP IV inhibitors are shown.



1 X = O Y = CH_2
2 X = O Y = S
3 X = S Y = CH_2
4 X = S Y = S



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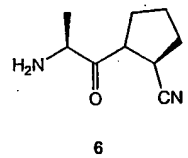

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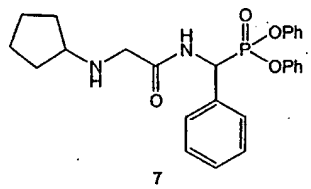

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Among these classes of inhibitors, some compounds have been reported to have some DPP II inhibitory activity, although with no selectivity with respect to DPP IV (Senten et al. *Biol. Med. Chem. Lett.*, 2002). The boronic acid dipeptide analogue Val-boroPro (5), used to inhibit QPP in the apoptosis studies (Chiravuri et al. J. Immunol. 1999, 163, 3092-3099) is in fact a more effective inhibitor for DPP IV (Table 1). Ala-pyrr-2-CN (6) was reported (Li et al. Arch. Biochem. Biophys., 1995, 323, 1, 148-154) as a weak inhibitor for DPP II, but also with higher potency toward DPP IV. Thiazolidides (2) are more effective DPP II inhibitors than the corresponding pyrrolidides (1) (Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31). The same argument, however, also serves for DPP IV inhibition. From a series with Ala, Phe, Val, Ile at P_2, Ile-Thia (2, Xaa = Ile) was the most potent DPP IV inhibitor, while Ile-Pyrr (1, Xaa = Ile) is the most selective DPP IV inhibitor with respect to DPP II. Thioxylation of the amide bond (3 and 4) gave different results for DPP II and DPP IV. Thioxylation increased DPP II inhibition up to 10 times, whereas thioamides are 20 times less efficient inhibitors for DPP IV than the corresponding amides (Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31). Thioamide analogues such as Ala ψ[CS-N]-Pyrr (3, Xaa = Ala) and Ala ψ[CS-N]-Thia (4, Xaa = Ala) are the only DPP II-DPP IV inhibitors described on this series to have some selectivity towards DPP II (Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31).

Incorporation of an electrophilic phosphonate group on the proline mimic at P_1 affords dipeptide proline diphenyl phosphonates, that are well known irreversible inhibitors of DPP IV. Recently, our laboratory reported a series of dipeptide α-aminoalkyl diphenyl phosphonates in which various P_1 diphenyl phosphonate building blocks were combined with commercially available or easily accessible amino acids. These compounds were used for the rapid profiling of DPP II. Most of these dipeptide diphenyl phosphonates gave DPP II inhibition to a moderate or high extent. *N*-cyclopentyl-$NH(C_6H_5)PO(OPh)_2$ (**7**) came out as the most selective and potent DPP II inhibitor (Senten et al. J. Comb. Chem., 2003).

Table 1 Inhibitory activity of DPP II inhibitors reported in literature

Compounds	DPP II/ QPP inhibition	DPP IV inhibition	SI[a]
1[b], Xaa = Ile	Ki = 24.7 μM	Ki = 0.218 μM	0.0088
2[b], Xaa = Ile	Ki = 8.17 μM	Ki = 0.126 μM	0.015
3[b], Xaa = Ala	K_I = 1.43 μM	K_I = 47.6 μM	33
4[b], Xaa = Ala	K_I = 0.277 μM	K_I = 7.88 μM	28
5[c]	K_I = 125 nM	K_I = 2 nM	0.016
6[d]	IC_{50} = 110 μM	K_I = 0.2 μM	
7[e]	IC_{50} = 3.8 μM	IC_{50} > 125 μM	> 33

[a]SI = selectivity index = value for DPP IV divided by value for DPP II.
[b]Values taken from Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31.
[c]Values taken from Underwood et al. J. Biol. Chem. 1999, 274, 48, 34053-34058
[d]Values taken from Li et al. Arch. Biochem. Biophys., 1995, 323, 1, 148-154.
[e]Values taken from Senten et al. J. Comb. Chem., 2003.

In this aspect of the invention the systematic search for a potent and selective DPP II inhibitor is reported, the structrure-activity relationship of several classes of inhibitors is reported. This aspect aims to identify lead compounds for the further development of highly selective and potent DPP II inhibitors.

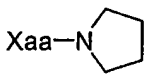
Chemistry

Most compounds reported in this example were rapidly prepared by parallel synthesis. Commercially available amino acids with tert-butyloxycarbonyl as α-amino protection and acid-labile side-chain protecting groups were coupled with the appropriate amine using a polymer-assisted solution-phase procedure as reported earlier (Senten et al. Tetrahedron Lett.., 2001, 42, 9135-9138). In this two step synthesis we were able to produce a large number of compounds without difficult purification steps. Some compounds, however, were purified before final deprotection by preparative TLC in order to assure the 95% purity needed for biological evaluation. Compounds 4 and 11 were prepared by thioxylation using

Lawesson's reagent after the parallel synthesis of the corresponding protected amides (Stöckel-Maschek et al. Biochim. Biophys. Acta, 2000, 1479, 15-31). Inhibitory activities for DPP IV of pyrrolidide analogues with different ring sizes, open ring structures and other homologues have been reported earlier (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309) These compounds (8) were now also evaluated for their DPP II inhibitory capacity (see formulas below). As standard P_2 amino acid L-Ile was used, although also several analogues were synthesised containing Lys as P_2 amino acid. The substituted pyrrolidides (9) were obtained by coupling of Boc protected amino acid (Ile or Lys) to 3-hydroxyproline. Various reactions at the hydroxyl function and cleavage of the protecting group resulted in the 3-substituted pyrrolidides (9, Table 4) (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309). An azide (9.3, 9.4) was obtained from a tosylate intermediate, prepared with tosylsulphonyl chloride and sodium azide. Treatment with benzoyl chloride afforded the benzoate (9.5, 9.6). Fluorine was introduced with diethylaminosulphur trifluoride (DAST. The synthesis of dipeptide nitriles (14, 15, 16, see formulas below) started by coupling Yaa-NH_2 and the required Boc protected amino acid, followed by dehydratation of the amide function to the nitrile using phosphorusoxychloride and subsequent acid catalysed deprotection.

Biochemical evaluation

To establish the most optimal N-terminal amino acid (P_2) for DPP II inhibition, we prepared a series of pyrrolidides (1). IC_{50} values for DPP II and DPP IV inhibition of compounds 1 are summarized in Table 2. A selectivity index is given as a means to evaluate the selectivity towards DPP IV. Lys-Pyrr (1.8) with an IC_{50} = 9.9 µM and His-Pyrr (1.6) exhibiting an IC_{50} = 1.16 µM came out as the most active DPP II inhibitors. These two compounds were also the most selective with respect to DPP IV. From this set of pyrrolidides (1) we can conclude that basic (Lys, 1.8) and neutral amino acids at P_2 are preferable over acidic amino acids. An acidic amino acid at this position seems not to be tolerated (Asp, 1.3), which is in agreement with the reported substrate specificity (Mentlein et al. J. Neurochem., 1989, 52, 1284-1293).



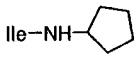
(1)

Table 2 Inhibitory activities and selectivity index of pyrrolidides (1)

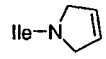
1.	Xaa	DPP II inhibition IC_{50} (μM)	DPP IV inhibition IC_{50} (μM)	SI[a]
1.1	Ala	179 ± 15	41 ± 6	0.2
1.2	Asn	152 ± 50	188 ± 6	1.2
1.3	Asp	> 500	122 ± 2	< 0.2
1.4	Cha[b]	42 ± 3	17 ± 2	0.4
1.5	Gly	> 1000	> 1000	1
1.6	His	1.2 ± 0.1	23.2 ± 1.0	20
1.7	Ile	110 ± 7	4 ± 1	0.04
1.8	Lys	9.9 ± 1.3	39 ± 2	3.9
1.9	Ser	65 ± 30	190 ± 120	2.9
1.10	Phe	79 ± 29	21 ± 4	0.3
1.11	Pro	> 500	15 ± 2	< 0.03
1.12	Thiapro	> 500	> 500	1
1.13	Tyr	150 ± 24	14 ± 2.4	0.09
1.14	Val	223 ± 13	4 ± 0.4	0.02

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.
[b]Cha = cyclohexylalanine.

In a quest for the optimal C-terminal residue (P_1-position), we replaced the pyrrolidine ring by several analogues such as pyrroline, thiazolidine, tetrahydropyridine, 4-, 6-, or 7-membered ring structures and acyclic amines, as indicated below.



8.1



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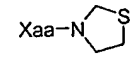
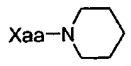
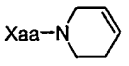


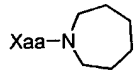
2.1 Xaa = Ile
2.2 Xaa = Lys



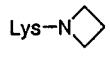
8.3 Xaa = Ile
8.4 Xaa = Lys



8.5 Xaa = Ile
8.6 Xaa = Lys



8.7 Xaa = Ile
8.8 Xaa = Lys



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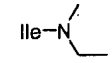

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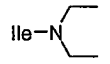

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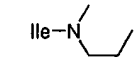


8.13

Results are summarized in Table 3. Ile was used as a standard P_2 amino acid. Lys identified as a good P_2 amino acid for more potent and selective DPP II inhibition, was also used in combination with the P_1 building blocks that revealed the most interesting results. The results

of these series 7 must be compared to Ile-Pyr (1.7) (IC_{50} for DPP II = 110 µM) and Lys-Pyrr (1.8) (IC_{50} for DPP II = 9.9 µM).

Table 3 Inhibitory activities and selectivity index for the above described compounds in series **8**

8.	DPP II inhibition IC_{50} (µM)	DPP IV inhibition IC_{50} (µM)	SI[a]
8.1	500	> 1000	> 2
8.2	288 ± 33	no data	
2.1	28 ± 9	1.7 ± 0.1	0.06
2.2	3 ± 0.3	318 ± 25	106
8.3	62 ± 27	67 ± 11	1.1
8.4	1.6 ± 0.3	247 ± 20	154
8.5	52 ± 3	52 ± 3	1
8.6	10.9 ± 1.0	> 500	> 46
8.7	173 ± 56	374 ± 62	2
8.8	51.9 ± 8.4	> 1000	19
8.9	159 ± 16	500 ± 25	3
8.10	> 1000	360 ± 18	< 0.4
8.11	> 500	167 ± 13	< 0.3
8.12	> 500	> 500	1
8.13	231 ± 10	377 ± 16	2

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.

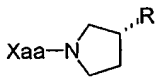
Taken the nitrogen out of the ring (8.1) or introducing a pyrroline ring (8.2), results in loss of DPP II as well as of DPP IV inhibition. This decrease in potency is also seen for the open structure pyrrolidides (8.10-8.13) and with introduction of 4- (8.9) or 7-membered (8.7, 8.8) rings. As already pointed out in the introduction thiazolidides have been reported to give an increase of both DPP II and DPP IV inhibition compared to the corresponding pyrrolidides. For the thiazolidides 2.1 and 2.2 the DPP II inhibition is increased with a factor 3 to 4, whereas inhibition of DPP IV increases slightly for Ile (2.1) in P_2, but decreases 8 times for Lys as P_2 amino acid. Lys-Thia (2.2) is 3 times more active DPP II inhibitor (IC_{50} = 3 µM) and far more selective towards DPP IV (SI = 106) than Lys-Pyrr (1.7). The expected increase of DPP IV inhibition that occurs in general with the replacement of pyrrolidine by thiazolidine is not seen for this compound.

Replacing the pyrrolidine ring by piperidine in 8.3 and 8.4, we can observe a 2 to 6-fold improvement of the DPP II inhibition. As reported earlier (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309), this introduction of a 6-membered ring gives a serious decrease in potency for DPP IV inhibitors. For DPP II inhibition, however, piperidine seems to be tolerated. Introducing a tetrahydropyridine in the P_1-position decreases as reported (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309) the DPP IV inhibition , but results

only in an improvement of DPP II inhibition for Ile (8.5) as P_2-amino acid, while with Lys (8.6) the DPP II inhibition is only slightly affected.

Lys-Pip (8.4) came out as the most potent DPP II-inhibitor in this series exhibiting an IC_{50} of 1.6 µM. This compound is also the most selective towards DPP IV with a selectivity index of 156.

To further explore the role of the P_1 position, some 3-substituted pyrrolidides (9.1-9.6- see table 4) were evaluated for their DPP II inhibitory potency. A two-fold increase of DPP II inhibition is seen for the azide substitent (9.3 and 9.4). Lys-Pyrr-3-N_3 has an IC_{50} of 4.9 µM and shows good selectivity towards DPP IV. With other substituents, the DPP II as well as the DPP IV inhibition decreases with exception of the fluorine. With this fluorine substituent (9.7), which is considered to be isosteric to a hydrogen, the inhibition of both enzymes is not affected.



(9)

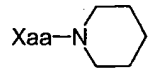
Table 4 Inhibitory activities and selectivity index of 3-substituted pyrrolidides (9)

9	Xaa	R	DPP II inhibition IC_{50} (µM)	DPP IV inhibition IC_{50} (µM)	SI[a]
9.1	Ile	OH	299 ± 2	93 ± 6	0.3
9.2	Lys	OH	48 ± 3	500 ± 25	10.4
9.3	Ile	N_3	43 ± 5	95 ± 7	2.2
9.4	Lys	N_3	4.9 ± 0.5	> 1000	> 205
9.5	Ile	$OC(O)C_6H_5$	158 ± 11	> 500	> 3.2
9.6	Lys	$OC(O)C_6H_5$	78.1 ± 7.8	> 1000	> 12.8
9.7	Ile	F	111 ± 10	3.5 ± 0.2	0.03

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.

From these series 8 and 9, it appears that for DPP II inhibition a broader variation in the P_1 position seems to be allowed, while for the inhibition of DPP IV the P_1-building block is restricted to pyrrolidine or thiazolidine. This conclusion can also be drawn from the earlier reported dipeptide α-aminoalkyl diphenyl phosphonates, where a broad set of various of P_1 phosphonate building blocks was introduced (Senten et al. J. Comb. Chem, 2003). Most of these compounds inhibited DPP II to a moderate or high extent, whereas little or no inhibition of DPP IV was observed.

Recognizing the importance of the piperidine ring, a broad series of Xaa-piperidides (**10**) was synthesised. Results are sumarized in Table 5. The significance of this piperidine ring is again confirmed: compared to the pyrrolidide series (**1**), an increase in DPP II inhibition up to 6 times is observed, whereas inhibition of DPP IV decreased simultanously with a factor between 6 and 17. Therefore, changing pyrrolidine to piperidine results in a considerable increase in potency and selectivity for DPP II. With basic amino acids (Arg (**10.1**), His (**10.3**), and Lys (**8.4**)), high DPP II inhibitory activities are observed.



(10)

Table 5 Inhibitory activities and selectivity index of piperidides (**10**)

10.	Xaa	DPP II inhibition IC_{50} (µM)	DPP IV inhibition IC_{50} (µM)	SI[a]
10.1	Arg	0.63 ± 0.11	18.1 ± 0.5	29
10.2	Cha[b]	9.9 ± 0.9	217 ± 13	22
10.3	His	0.33 ± 0.06	213 ± 42	704
8.3	Ile	62 ± 27	67 ± 11	1.1
10.4	Ser	21.7 ± 0.8	> 1000	46
8.4	Lys	1.6 ± 0.3	247 ± 20	154
10.5	Lys(Z)	2.1 ± 0.2	134.9 ± 1.2	64
10.6	Orn	0.45 ± 0.08	> 500	> 1111
10.7	Dab[c]	0.13 ± 0.01	> 1000	> 7592
10.8	D-Dab	130 ± 5	>> 1000	>> 8
10.9	Dab(Z)	1.15 ± 0.08	500 ± 25	435
10.10	Z-Dab			
10.11	Dap[d]	1.84 ± 0.13	> 1000	> 544
10.12	Abu[e]	88.7 ± 7.3	250 ± 25	2.8
10.13	Nva[f]	57.1 ± 3.9	229 ± 44	4
10.14	Nle[g]	32.4 ± 2.7	250 ± 25	8

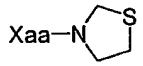
[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.
[b]Cha = cyclohexylalanine
[c]Dab = 2,4-diaminobutyric acid
[d]Dap = 2,3-diaminopropionic acid
[e]Abu = 2-aminobutyric acid
[f]Nva = norvaline
[g]Nle = norleucine

The side chain length ($(CH_2)_nNH_2$) in Lys-Pip is investigated by replacing the P_2 amino acid lysine (n = 4) (8.4) with respectively ornithine (n = 3) (10.6), 2,4-diaminobutyric acid (n = 2) (10.7) and 2,3-diaminopropionic acid (n = 1) (10.11). Decreasing the side chain length to n = 2 enhanced the DPP II inhibitory potency. Further decrease of the side chain revealed a reduction in potency (10.11, n = 1). Also selectivity was significantly improved since inhibition

of DPP IV declined tremendously with decreasing side chain length. Dab-Pip (10.7) with an IC_{50} = 0.13 μM and a selectivity index of more than 7000 is the most active and most selective DPP II inhibitor in this series.

Blocking the side chain amino function in Lys-Pip and Dab-Pip with benzyloxycarbonyl (10.5, 10.9 respectively) afforded for Dab(Z)-Pip (10.9) a decrease in potency up to 9 times, whereas selectivity was reduced here by a factor 17. The significance of this side chain amino function is also revealed in compounds 10.12 to 10.14 where this amino function is omitted: the DPP II inhibition is decreased tremendously and these compounds show no selectivity at all towards DPP IV. The highest potency here is observed with 10.14 (n = 3, IC_{50} = 32.4 μM) and decreases slightly with decreasing chain length ($(CH_2)_nCH_3$). From compounds 10.5, 10.9 and 10.12 to 10.14 we can assume that basic amino acids in P_2 are preferable for DPP II inhibition, but moreover might be necessary to introduce selectivity. With *D*-Dab-PiP (10.8) the importance of the L-configuration of the P_2-amino acid for DPP II inhibition is confirmed, like is seen for DPP IV inhibition: a 1000-fold decrease in DPP II inhibitory activity is noticed.

The series of thiazolidides (2) (Table 6) was completed by combining thiazolidine with some interesting P_2 amino acids from the previous series 10. In general, we observe for this Xaa-Thiazolidides compared to the pyrrolidide series (1) an enhancement in DPP II as well as in DPP IV inhibition with the exception of Lys-Thia (2.2) where DPP IV inhibition declined 8 times. Compared to the corresponding piperidides (10), these Xaa-thiazolidides (2) are no better DPP II inhibitors: depending on the P_2 amino acid only a slight decrease or increase of the DPP II inhibition is observed. Selectivity, however, is significantly affected: for all these compounds the selectivity index decreased 2 to 22 times. Thiazolidides (2) are therefore less selective DPP II inhibitors compared to the corresponding piperidides (10).



(2)

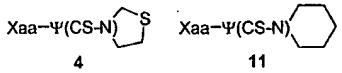
Table 6 Inhibitory activities and selectivity index of thiazolidides (2)

2.	Xaa	DPP II inhibition IC_{50} (μM)	DPP IV inhibition IC_{50} (μM)	SI[a]
2.1	Ile	28 ± 9	1.7 ± 0.1	0.06
2.2	Lys	3 ± 0.3	318 ± 25	106
2.3	Orn	0.75 ± 0.02	81 ± 2	108
2.4	Dab[b]	0.14 ± 0.01	289 ± 8	2064

2.5	Cha[c]	8.3 ± 0.5	8.5 ± 0.3	1.02

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.
[b]Dab = 2,4-diaminobutyric acid
[c]Cha = cyclohexylalanine

Thioxylation of the amide bond in Lys-thiazolidide leading to 4.1 (Table 6) afforded as expected a higher inhibition of DPP II. However, inhibition of DPP IV increased, which is in contrast with previous reports. Thioamides of some Xaa-piperidides are summarized in Table 7. In this series of Xaa Ψ[CS-N]-piperidides (11) dubious results are seen. Lys Ψ[CS-N]-piperidide (11.5) with an IC_{50} = 0.49 μM and a selectivity index of more than 2000 is an important progress compared to the corresponding amide Lys-Pip (8.4). We see a 3-fold increase in DPP II inhibitory potency while selectivity is greatly enhanced by a factor 13. Unfortunately, this increase in DPP II inhibition and selectivity as a result of thioxylation, is not seen with thioxylation of the more potent Dab-PiP (10.7). Dab Ψ[CS-N]-piperidide (11.3) exhibited an IC_{50} = 0.22 μM and is therefore a less active DPP II inhibitor compared to Dab-Pip (10.7). Selectivity is also declined although a selectivity index of more than 4000 can still be considered high.



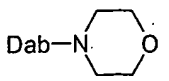
4 11

Table 7 Thioxylated amides (**4, 11**)

4 or 11	Xaa	DPP II inhibition IC_{50} (μM)	DPP IV inhibition IC_{50} (μM)	SI[a]
4.1	Lys	0.71 ± 0.05	44.2 ± 1	62
11.1	Cha[b]	8.0 ± 0.6	1000	125
11.2	Ile	16.7 ± 0.5	23.9 ± 1.3	1.4
11.3	Dab[c]	0.22 ± 0.01	> 1000	> 4484
11.4	Orn	0.2 ± 0.1	> 1000	> 5050
11.5	Lys	0.49 ± 0.02	> 1000	> 2041

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.
[b]Cha = cyclohexylalanine
[c]Dab = 2,4-diaminobutyric acid

Having identified Dab-Pip (10.7) as the most potent and selective inhibitor, some analogues were prepared by replacing the piperidine ring with respectively morfoline (12) and piperazine (13) (Table 8). The DPP II inhibitory activity is declined tremendously for Dab-piperazide (13), whereas for Dab-morfolide (12) the DPP II inhibition is decreased with a factor 4 and can still be considered as a potent DPP II inhibitor with a IC_{50} = 0.51 μM.



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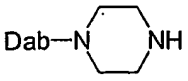


(13)

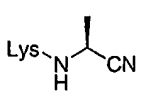
Table 8 Inhibitory activities and selectivity index of Dab-Pip analogues

	DPP II inhibition IC_{50} (μM)	DPP IV inhibition IC_{50} (μM)	SI[a]
12	0.51 ± 0.02	> 1000	> 1961
13	29.3 ± 1.7	> 1000	> 34

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.

Aminoacylpyrrolidide-2-nitriles are slow-binding, reversible inhibitors of DPP IV with approximately a 1000-fold increase in potency compared to the parent amino acyl pyrrolidides (low nM K_i) and a more than 500-fold selectivity against DPP II (Li et al. Arch. Biochem. Biophys., 1995, 323, 1, 148-154). However, we investigated some dipeptide nitriles (14,15,16) for their DPP II inhibitory activity. The formulas for synthesised dipeptide nitriles (14, 15, 16) are provided below. Based on the frequently used Lys-Ala chromogenic substrate for measurement of DPP II activity, Lys-Ala-CN (14) was prepared. This compound (14) inhibits DPP II to a certain magnitude (IC_{50} = 84 μM) while a minimal DPP IV inhibition is observed. The cyanopyrrolidide analogue, Lys-Pyrr-2-CN (15) inhibited DPP II to a greater extent (IC_{50} = 1.0 μM), but appeared indeed to be a better inhibitor for DPP IV (IC_{50} = 0.30 μM). The selectivity could be reversed by replacing the pyrrolidine ring with piperidine. Compared to 15, Lys-Pip-2-CN (16.1) only slightly affect the DPP II inhibition while inhibitory activity of DPP IV declined with a factor 160. Compound 16.1 is therefore a more selective DPP II inhibitor compared to the cyanopyrrolidide analogue (15). However in comparison with Lys-Pip (8.4), no improvement in DPP II inhibitory potency is observed and is accompagnied by a 4-fold decrease in selectivity. It must be noticed that for this compound a mixture of diastereomers was tested: the inactive *L*-Lys-Pip-2(*R*)-CN and biological active *L*-Lys-Pip-2(S)-CN isomer.

Incorporation of a nitrile in Dab-Pip (10.7) enhanced the inhibition of DPP II with a factor 5. Dab-Pip-2-CN (16.2) exhibited an IC_{50} = 46 nM and can be regarded as the most active DPP II inhibitor in our investigation. However, for this compound (16.2) the selectivity index declined as well and is therefore less selective with respect to DPP IV compared to Dab-Pip (10.7).



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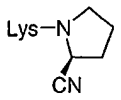

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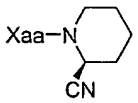


16.1 Xaa = Lys
16.2 Xaa = Dab

Table 9 Inhibitory activities and selectivity index of dipeptide nitriles (**14**, **15** and **16**).

	DPP II inhibition IC_{50} (μM)	DPP IV inhibition IC_{50} (μM)	SI[a]
14	84 ± 14	> 500	> 6
15	1.0 ± 0.3	0.32 ± 0.03	0.32
16.1[b]	1.48 ± 0.09	51.2 ± 1.8	35
16.2[c]	0.046 ± 0.005	151.9 ± 6.3	3274

[a]SI = selectivity index= IC_{50} value for DPP IV divided by IC_{50} value for DPP II.
[b]The compound tested was *L*-Lys-Pip-2(*R,S*)-CN.

In conclusion, for DPP IV inhibition a significant increase in potency is seen for the 2-cyanopyrrolidides compared to the corresponding pyrrolidides. However, the increase in DPP II inhibition is not as distinct when going from piperidides to 2-cyanopiperidides. These investigated 2-cyanopiperidides (16.1, 16.2) turned out to be less selective regarding to DPP IV than the parent piperidides.

In this example we were able to identify the most optimal N-terminal and C-terminal residue for potent and selective DPP II inhibition. Dab was selected as the most promising N-terminal amino acid with regard to DPP II inhibition and selectivity. The basic side chain amino function was proved to be essential for selective DPP II inhibition. Omitting this function or making it less basic by blocking it, decreased DPP II inhibitory potency and more important, the selectivity was negatively affected. In the quest for the most optimal P_1 building block; piperidine was recognised as being superior over pyrrolidine and thiazolidine. Amino acyl thiazolidides (2) were more or less equipotent as DPP II inhibitors compared to the corresponding piperidides (10), but are regarded as less selective with respect to DPP IV.

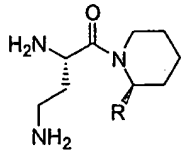
In this example, we observed that the nature of the P_1 residue is less stringent for DPP II inhibition than it is for DPP IV inhibition. For DPP IV inhibition only pyrrolidide or thiazolidide is tolerated, while a large variety of P_1 building blocks was allowed for DPP II inhibition, blocking this enzyme to a moderate or high extent.

Dab-Pip (10.7) has an IC_{50} = 130 nM and a selectivity index of more than 7000. Incorporation of a nitrile, leading to Dab-Pip-2-CN (16.2), increased potency with a factor 5. However, the

selectivity index of this nitrile compound (16.2) declined to 3000 and is therefore less selective than compound 10.7. Both compounds are the most active and selective DPP II inhibitors reported to date. The high selectivity of these two compounds (10.7 and 16.2) must be emphasised. Val-Pyrr (1), identified as the most selective DPP IV inhibitor, is recently used in animal studies to evaluate the effects of DPP IV inhibitors in the treatment of type II diabetes. However, the IC_{50} value for DPP IV is only 56-fold lower than for DPP II and the selectivity towards DPP II can therefore be regarded as limited. One can argue if its selectivity is sufficient to study the role of DPP IV in biological systems. In this respect the Pro-Pro diaryl phosphonates reported (Belyaev et al. J. Med. Chem., 1999, 42, 1041-1052) by our group, with very low DPP II inhibitory activity, seem a better choice to selectively inhibit DPP IV.

These two compounds (10.7 and 16.2) may offer the opportunity to study the physiological role of DPP II and possible therapeutic benefits of DPP II inhibition. Their high selectivity will enable to differentiate between DPP II and DPP IV in biological systems. Both compounds can also serve as lead compounds for further development of DPP II inhibitors in our laboratory.

According to this example, the structures of the most potent and selective DPP II inhibitors are the following:



10.7 R = H
16.2 R = CN

Experimentally, for preparing the compounds represented in this example, parallel synthesis was performed using the Quest 210 Organic Synthesizer (Argonaut Technologies). Boc-protected amino acids, N-cyclohexycarbodiimide, N'-methylpolystyrene resin (PS-carbodiimide) and tris-(2-aminoethyl)-amine polystyrene resin were purchased from Novabiochem. Other reagents were obtained from Sigma-Aldrich or Acros. Compounds 8.1, 8.2, 8.5, 8.7, 8.10-8.13, 9.1, 9.3, 9.5, 9.7 were synthesised as reported earlier (Augustyns et al. Eur. J. Med. Chem., 1997, 32, 301-309).

Analysis

Characterisation of all compounds was done with ^{1}H-NMR and mass spectrometry. ^{1}H-NMR were recorded on a Bruker Avance DRX-400 spectrometer (400 MHz). Fast Atom Bombardement (FAB^+) mass spectra were obtained on a VG 70-SEQ hybrid mass spectrometer (Micromass, Manchester, UK), equipped with a cesium ion gun. Electrospray (ES^+) mass spectra were acquired on a Autospec-ao-TOF mass spectrometer (Micromass, Manchester, UK) or a tripple quadrople mass spectrometer (Quattro II, Micromass, Manchester, UK) or a Bruker Esquire 3000 plus mass spectrometer. Purity was verified using two diverse HPLC systems using respectively mass and uv-detection. LC-MS were recorded on a Agilent 1100 Series HPLC system using a Discovery Cyano column (2.1 x 50 mm, 5µm, Supelco, Sigma-Aldrich) coupled with a Bruker Esquire 3000 plus mass spectrometer (0-80% ACN, 22 min, 0.2 ml/min). Reverse phase HPLC was run on a Gilson instrument (Viliers-le-bel, France) equipped with an Ultrasphere ODS column (4.6 x 250 mm, 5 µm, Beckman, Fullerton, CA, USA) and a uv-detector (10-100% ACN, 35 min, 214 nm, 1 ml/min). Preparative TLC was performed on Silicagel $60PF_{254}$ containing gypsum.

Biochemical Evaluation

DPP IV was purified from human seminal plasma as described previously (De Meester et al. J. Immunol. Methods 1996, 189, 99 105). DPP II was isolated from the same source using techniques described previously for purification of the enzyme from porcine seminal plasma (Huang et al. Biochim. Biophys. Acta 1996, 1290, 149 156), supplemented with adenosine deaminase affinity chromatography to eliminate contaminating DPP IV(De Meester et al. J. Immunol. Methods 1996, 189, 99 105). Enzyme activity was measured kinetically with the chromogenic substrates Gly-Pro-p-nitroanilide at pH 8.3 and Lys-Ala-p-nitroanilide at pH 5.5 for DPP IV and DPP II respectively. Test compounds were dissolved and diluted in DMSO (final concentration DMSO during assay 5% v/v). Highest concentration of compounds tested is 1 mM. IC_{50} value was defined as the inhibitor concentration, which caused a 50% decrease of the activity under assay conditions.

General procedure for synthesis of compounds 1, 2, 4, 8.3-8.9, 10, 11, 12 and 13.

These series were prepared by parallel synthesis using a PASP-protocol Senten et al. *Tetrahedron Lett..*, 2001, *42*, 9135-9138): protected amino acids (0.375 mmol), HOBt (0.425 mmol) and PS-Carbodiimide (0.75 mmol) were added to a dry reaction vessel. Dichloromethane (4 ml) was added and the mixture was stirred for 10 min prior to the addition

of the appropriate amine (respectively pyrrolidine (1), thiazolidine (2, 4), 1,2,5,6-tetrahydropyridine (8.5, 8.6), hexamethyleneimine (8.7, 8.8), azetidine (8.9), piperidine (10, 11), morfoline (12) and Boc-piperazine (13)). After stirring at room temperature overnight the polymer-bound polyamine (1.5 mmol) was added and stirring was continued for 5 h. The reaction mixture was filtered and the amide product was collected in the filtrate. The resins are washed two times with 4 ml of dichloromethane and the combined fractions were evaporated under reduced pressure. The purity of the compounds was checked by TLC and reverse phase HPLC. Compounds were purified by preparative TLC using a mixture of EtOAc and hexane (usually 40/60) as eluent.

General procedure for *tert*-bytyloxycarbonyl (Boc) –deprotection

Deprotection was done by dissolving in 4 ml of a TFA/dichloromethane (1:1) mixture. The solution was stirred for 3 h and the volatile part was removed under reduced pressure. After coevaporating several times with ether, the residues were lyophilised from *tert*-butanol/water (4:1).

1-(L-Alanyl)pyrrolidine trifluoroacetate (1.1)

^{1}H-NMR (D_2O, 400 MHz) δ 1.44 (d, 3H, CH_3), 1.84-1.97 (m, 4H, CH_2), 3.34-3.56 (m, 4H, CH_2), 4.26 (m, 1H, α-CH); MS (ES^+) m/z 143 $(M + H)^+$.

1-(L-Asparaginyl)pyrrolidine trifluoroacetate (1.2).

^{1}H-NMR (D_2O, 400 MHz) δ 1.78-1.95 (m, 4H, CH_2), 2.71 (dd, 1H, CH_2), 2.84 (dd, 1H, CH_2), 3.28-3.56 (m, 4H, CH_2), 4.47 (t, 1H, α-CH); MS (FAB^+) m/z 186 $(M + H)^+$.

1-(L-Aspartyl)pyrrolidine trifluoroacetate (1.3).

^{1}H-NMR (D_2O, 400 MHz) δ 1.84-1.97 (m, 4H, CH_2), 2.86 (dd, 1H, CH_2), 3.02 (dd, 1H, CH_2), 3.36-3.59 (m, 4H, CH_2), 4.54 (t, 1H, α-CH); MS (FAB^+) m/z 186 $(M + Na)^+$.

1-(S-Cyclohexylalanyl)pyrrolidine trifluoroacetate (1.4).

^{1}H-NMR (DMSO-d_6), 400 MHz) δ 0.70-2.00 (m, 17H, CH_2, CH), 3.20-3.70 (m, 4H, CH_2), 3.95-4.10 (m, 1H, α-CH), 8.30 (brs, 3H, NH_3^+); MS (FAB^+) m/z 224 $(M + Na)^+$.

1-(L-Glycyl)pyrrolidine trifluoroacetate (1.5).

^{1}H-NMR (D_2O, 400 MHz) δ 1.82-1.98 (m, 4H, CH_2), 3.36-3.42 (m, 4H, CH_2), 3.86 (s, 2H, CH_2); MS (ES^+) m/z 129 $(M + H)^+$.

1-(L-Histidyl)pyrrolidine ditrifluoroacetate (1.6).

^{1}H-NMR (D_2O, 400 MHz) δ 1.90-2.01 (m, 4H, CH_2), 3.22-3.28 (m, 1H, β-CH_2), 3.44-3.57 (m, 4H, CH_2), 3.64-3.69 (m, 1H, β-CH_2), 4.65 (t, 1H, α-CH), 7.52 (s, 1H, 4H-His), 8.78 (s, 1H, 2H-His); MS (ES^+) m/z 209 $(M + H)^+$.

1-(L-Isoleucyl)pyrrolidine ditrifluoroacetate (1.7).

^{1}H-NMR (DMSO-d_6, 250 MHz) δ 0.85 (t, 3H, δ-CH_3), 0.93 (d, 3H, γ-CH_3), 1.05-1.20 (m, 1H, γ-CH_2), 1.40-1.60 (m, 1H, γ-CH_2), 1.70-2.00 (m, 5H, β-CH, CH_2), 3.25-3.70 (m, 4H, CH_2), 3.93 (m, 1H, α-CH), 8.14 (s, 3H, NH_3^+); MS (FAB^+) m/z 185 $(M + Na)^+$.

1-(L-Lysyl)pyrrolidine ditrifluoroacetate (1.8).

^{1}H-NMR (D_2O, 400 MHz) δ 1.42-1.48 (m, 2H, CH_2), 1.63-1.71 (m, 2H, CH_2), 1.83-2.00 (m, 6H, β-CH_2, CH_2), 2.96 (t, 2H, ε-CH_2), 3.35-3.60 (m, 4H, CH_2), 4.26 (t, 1H, α-CH); MS (ES^+) m/z 200 $(M + H)^+$.

1-(L-Seryl)pyrrolidine trifluoroacetate (1.9).

^{1}H-NMR (D_2O, 400 MHz) δ 1.78-1.95 (m, 4H, CH_2), 3.32-3.56 (m, 4H, CH_2), 3.81 (dd, 1H, CH_2), 3.90 (dd, 1H, CH_2), 4.29 (t, 1H, α-CH); MS (FAB^+) m/z 159 $(M + H)^+$.

1-(L-Phenylalanyl)pyrrolidine trifluoroacetate (1.10).

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.78 (m, 4H, CH_2), 2.56-2.62 (m, 1H, CH_2), 3.06-3.19 (m, 2H, CH_2), 3.24-3.39 (m, 3H, CH_2), 4.42 (t, 1H, α-CH), 7.21 (m, 2H, o-H_{arom}), 7.31-7.38 (m, 3H, m-, p-H_{arom}); MS (ES^+) m/z 219 $(M + H)^+$.

1-(L-Prolyl)pyrrolidine trifluoroacetate (1.11).

^{1}H-NMR (D_2O, 400 MHz) δ 1.86-2.07 (m, 7H, β-CH_2-, γ-CH_2, CH_2), 2.45-2.54 (m, 1H, β-CH_2), 3.31-3.56 (m, 6H, δ-CH_2, CH_2), 4.51 (t, 1H, α-CH); MS (ES^+) m/z 169 $(M + H)^+$.

1-(S-Thiaprolyl)pyrrolidine trifluoroacetate (1.12).

^{1}H-NMR (D_2O, 400 MHz) δ 1.86–2.01 (m, 4H, CH_2), 3.17 (dd, 1H, β-CH_2), 3.37–3.59 (m, 4H, CH_2), 3.63 (m, 1H, β-CH_2), 4.39 (d, 1H, δ-CH_2), 4.48 (d, 1H, δ-CH_2), 4.75-4.84 (m, 1H, α-CH); MS (ES^+) m/z 187 $(M + H)^+$.

1-*(L-Tyrosyl)pyrrolidine trifluoroacetate (1.13).*

^{1}H-NMR (D_2O, 400 MHz) δ 1.51-1.80 (m, 4H, CH_2), 2.56-2.62 (m, 1H, CH_2), 2.98-3.14 (m, 2H, CH_2), 3.24-3.40 (m, 3H, CH_2), 4.37 (t, 1H, α-CH), 6.84 (d, 2H, 3-,5-H_{arom}), 7.12 (d, 2H, 2-,6-H_{arom}); MS (ES^+) m/z 235 $(M + H)^+$.

1-(L-Valyl)pyrrolidine trifluoroacetate (1.14).

^{1}H-NMR (D_2O, 400 MHz) δ 0.97 (d, 3H, CH_3), 1.02 (d, 3H, CH_3), 1.82-1.98 (m, 4H, CH_2), 2.18-2.26 (m, 1H, β-CH_2), 3.38-3.60 (m, 4H, CH_2), 4.06 (d, 1H, α-CH); MS (ES^+) m/z 171 $(M + H)^+$.

1-(L-Isoleucyl)thiazolidine trifluoroacetate (2.1).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.9-1.38 (m, 7H, CH_3, CH_2), 1.52-1.67 (m, 1H, CH_2), 1.90-2.02 (m, 1H, CH), 2.98-3.15 (m, 2H, 5-CH_2), 3.69-3.80 (m, 1H, 4-CH_2), 3.88-4.02 (m, 1H, 4-CH_2), 4.12-4.23 (m, 1H, α-CH), 4.41-4.68 (m, 2H, 2-CH_2); MS (ES^+) m/z 203 $(M + H)^+$.

1-(L-Lysyl)thiazolidine trifluoroacetate (2.2).

^{1}H-NMR (D_2O, 400 MHz) δ 1.81-2.11 (m, 6H, CH_2), 3.15-3.29 (m, 4H, ε-CH_2, 5-CH_2), 3.82-4.04 (m, 2H, 4-CH_2), 4.60-4.82 (m, 3H, 2-CH_2, α-CH); MS (ES^+) m/z 218 $(M + H)^+$.

1-(S-Ornithyl)thiazolidine trifluoroacetate (2.3).

^{1}H-NMR (D_2O, 400 MHz) δ 1.83-1.91 (m, 2H, γ-CH_2), 2.05-2.10 (m, 2H, β-CH_2), 3.12 (t, 2H, 5-CH_2), 3.20 (t, 1H, δ-CH_2), 3.27 (t, 1H, δ-CH_2), 3.83-4.08 (m, 2H, 4-CH_2), 4.52 (t, 0.5H, α-CH), 4.57 (t, 0.5H, α-CH), 4.59-4.84 (m, 2H, 2-CH_2); MS (ES^+) m/z 203 $(M + H)^+$.

1-(S-2,4-Diaminobutanoyl)thiazolidine trifluoroacetate (2.4).

^{1}H-NMR (D_2O, 400 MHz) δ 2.34-2.40 (m, 2H, β-CH_2), 3.18-3.28 (m, 4H, γ-CH_2, 5-CH_2), 3.84-4.07 (m, 2H, 4-CH_2), 4.55-4.84 (m, 3H, 2-CH_2, α-CH); MS (ES^+) m/z 190 $(M + H)^+$.

1-(S-Cyclohexylalanyl)thiazolidine trifluoroacetate (2.5).

^{1}H-NMR (D_2O, 400 MHz) δ 0.84-2.05 (m, 13H, CH_2, CH), 3.02-3.16 (m, 2H, 5-CH_2), 3.84-4.07 (m, 2H, 4-CH_2), 4.20-4.25 (m, 1H, α-CH), 4.41-4.68 (m, 2H, 2-CH_2); MS (ES^+) m/z 243 $(M + H)^+$.

1-(L-Lysyl)-1,2,5,6-tetrahydropyridine trifluoroacetate (8.6).

^{1}H-NMR (D_2O, 400 MHz) δ 1.45-1.55 (m, 2H, CH_2), 1.69-1.81 (m, 2H, CH_2), 1.91-2.00 (m, 2H, CH_2), 2.23-2.36 (m, 2H, 5-CH_2), 3.05 (b, 2H, ε-CH_2), 3.62-3.81 (m, 2H, 6-CH_2), 4.03-4.17 (m, 2H, 2-CH_2), 4.55 (t, 0.5H, α-CH), 4.62 (t, 0.5H, α-CH), 5.75-5.82 (m, 1H, 4-CH), 5.96-6.06 (m, 1H, 3-CH); MS (ES^+) m/z 212 $(M + H)^+$.

1-(L-Lysyl)hexamethyleneimine trifluoroacetate (8.8).

^{1}H-NMR (D_2O, 400 MHz) δ 1.51-1.66 (m, 6H, CH_2), 1.72-1.86 (m, 6H, CH_2), 1.94-2.00 (m, 2H, CH_2), 3.06 (t, 2H, ε-CH_2), 3.39-3.56 (m, 2H, CH_2), 3.62-3.74 (m, 2H, CH_2), 4.53 (t, 1H, α-CH); MS (ES^+) m/z 228 $(M + H)^+$.

1-(L-Lysyl)azetidine trifluoroacetate (8.9).

^{1}H-NMR (D_2O, 400 MHz) δ 1.43-1.57 (m, 2H, CH_2), 1.70-1.80 (m, 2H, CH_2), 1.85-1.96 (m, 2H, CH_2), 2.35-2.48 (m, 2H, 3-CH_2), 3.05 (br s, 2H, ε-CH2), 4.06-4.29 (m, 3H, CH_2, α-CH), 4.39-4.44 (m, 1H, 3-CH); MS (ES^+) m/z 186 $(M + H)^+$.

1-(L-Arginyl)piperidine ditrifluoroacetate (10.1).

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.80 (m, 8H, CH_2), 1.92-2.00 (m, 2H, CH_2), 3.25-3.38 (m, 2H, δ-CH_2), 3.44-3.77 (m, 4H, CH_2), 4.60-4.70 (m, 1H, α-CH); MS (ES^+) m/z 242 $(M + H)^+$; LC-MS rt 0.4-0.5 min, m/z 242 $(M + H)^+$; UV-HPLC rt 4.58 min, 91%.

1-(S-Cyclohexylalanyl)piperidine trifluoroacetate (10.2).

^{1}H-NMR (D_2O, 400 MHz) δ 0.91-1.79 (m, 19H, CH_2), 3.40-3.53 (m, 4H, 2-CH_2, 6-CH_2), 4.49 (t, 1H, α-CH); MS (ES^+) m/z 239 $(M + H)^+$; LC-MS rt 1.0-1.4 min, m/z 239 $(M + H)^+$; UV-HPLC rt 23.49 min, 100%.

1-(L-Histidyl)piperidine ditrifluoroacetate (10.3).

^{1}H-NMR (D_2O, 400 MHz) δ 1.52-1.79 (m, 6H, 3-CH_2, 4-CH_2, 5-CH_2), 3.31-3.72 (m, 6H, β-CH_2, 2-CH_2, 6-CH_2), 4.81-4.93 (m, 1H, α-CH), 7.54 (s, 1H, 4-CH-His), 8.81 (s, 1H, 2-CH-His); MS (ES^+) m/z 223 $(M + H)^+$; LC-MS rt 0.3-0.5 min, m/z 223 $(M + H)^+$; UV-HPLC rt 4.04 min, 88%.

1-(L-Isoleucyl)piperidine trifluoroacetate (8.3).

^{1}H-NMR (DMSO-d_6, 400 MHz) δ 0.85 (t, 3H, δ-CH_3), 0.94 (d, 3H, γ-CH_3), 1.00-1.25 (m, 1H, γ-CH), 1.35-1.70 (m, 7H, γ-CH, 3-CH_2, 4-CH_2, 5-CH_2), 1.70-1.85 (m, 1H, β-CH), 3.20-3.65 (m, 4H, 2-CH_2, 6-CH_2), 4.25 (d, 1H, α-CH), 8.07 (br s, 3 H, NH_3+); MS (ES^+) m/z 199 $(M + H)^+$; LC-MS rt 0.6-0.7 min, m/z 199 $(M + H)^+$; UV-HPLC rt 11.30 min, 100%.

1-(L-Seryl)piperidine trifluoroacetate (10.4).

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.73 (m, 6H, CH_2), 3.50-3.64 (m, 4H, CH_2), 3.90-3.95 (m, 1H, β-CH_2), 4.02-4.06 (m, 1H, β-CH_2), 4.62-4.68 (m, 1H, α-CH); MS (ES^+) m/z 173 $(M + H)^+$; LC-MS rt 0.5-0.6 min, m/z 173 $(M + H)^+$; UV-HPLC rt 4.91 min, 93%.

1-(L-Lysyl)piperidine ditrifluoroacetate (8.4).

^{1}H-NMR (D_2O, 400 MHz) δ 1.34-1.87 (m, 12H, CH_2), 2.95 (t, 2H, ε-CH_2), 3.43-3.53 (m, 4H, CH_2), 4.50 (t, 1H, α-CH), MS (ES^+) m/z 214 $(M + H)^+$; LC-MS rt 0.3-0.5 min, m/z 214 $(M + H)^+$; UV-HPLC rt 2.59 min, 86%.

1-(N-ε-(Benzyloxycarbonyl)-L-Lysyl)piperidine ditrifluoroacetate (10.5).

^{1}H-NMR (D_2O, 400 MHz) δ 1.37-1.76 (m, 10H, CH_2), 1.84-1.98 (m, 2H, CH_2), 3.14-3.28 (m, 2H, ε-CH_2), 3.41-3.68 (m, 4H, CH_2), 4.47-4.57 (m, 1H, α-CH), 5.11-5.26 (m, 2H, CH_2-Z), 7.49 (s, 5H, H_{arom}); MS (ES^+) m/z 348 $(M + H)^+$; LC-MS rt 1.6-1.9 min, m/z 348 $(M + H)^+$; UV-HPLC rt 14.59 min, 100%.

1-(S-Ornithyl)piperidine ditrifluoroacetate (10.6).

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.91 (m, 8H, CH_2), 1.97-2.03 (m, 2H, CH_2), 3.11 (t, 2H, δ-CH_2), 3.53-3.66 (m, 4H, CH_2), 4.66 (t, 1H, α-CH); MS (ES^+) m/z 200 $(M + H)^+$; LC-MS rt 0.4-0.6 min, m/z 200 $(M + H)^+$; UV-HPLC rt 3.74 min, 100%.

1-(S-2.4-Diaminobutanoyl)piperidine ditrifluoroacetate (10.7)).

^{1}H-NMR (D_2O, 400 MHz) δ 1.59-1.73 (m, 6H, CH_2), 2.27-2.34 (m, 2H, β-CH_2), 3.12-3.23 (m, 2H, γ-CH_2), 3.50-3.71 (m, 4H, CH_2), 4.72 (t, 1H, α-CH); MS (ES^+) m/z 186 $(M + H)^+$; LC-MS rt 0.5-0.6 min, m/z 186 $(M + H)^+$; UV-HPLC rt 3.62 min, 100%.

1-(D-2.4-diaminobutanoyl)piperidine ditrifluoroacetate (10.8).

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.62 (m, 6H, CH_2), 2.15-2.21 (m, 2H, β-CH_2), 3.02-3.11 (m, 2H, γ-CH_2), 3.41-3.59 (m, 4H, CH_2), 4.61 (t, 1H, α-CH); MS (ES^+) m/z 186 $(M + H)^+$; LC-MS rt 0.4-0.5 min, m/z 186 $(M + H)^+$; UV-HPLC rt 4.66 min, 100%.

1-(S-2,4-benzyloxycarbonyl-diaminobutanoyl)piperidine trifluoroacetate (10.9).

^{1}H-NMR (D_2O, 400 MHz) δ 1.20-1.71 (m, 6H, CH_2), 1.85-2.05 (m, 2H, β-CH_2), 3.29-3.55 (m, 6H, CH2, γ-CH_2), 4.44 (m, 1H, α-CH), 5.13 (s, 2H, CH_2), 7.43 (s, 5H, H_{arom}); MS (ES^+) m/z 320 $(M + H)^+$; LC-MS rt 1.1-1.2 min, m/z 320 $(M + H)^+$; UV-HPLC rt 14.85 min, 97%.

1-(S-2-benzyloxycarbonyl,4-diaminobutanoyl)piperidine trifluoroacetate (10.10).

^{1}H-NMR (D_2O, 400 MHz) δ 1.41-1.71 (m, 6H, CH_2), 1.98-2.17 (m, 2H, β-CH_2), 3.02-3.76 (m, 6H, γ-CH_2, CH_2), 4.70-4.85 (m, 1H, α-CH), 5.17 (s, 2H, CH_2), 7.46 (s, 5H, H_{arom}); MS (ES^+) m/z 320 $(M + H)^+$; LC-MS rt 0.4-0.6 min, m/z 320 $(M + H)^+$; UV-HPLC rt 14.48 min, 96%.

1-(S-2.3-diaminopropanoyl)piperidine ditrifluoroacetate (10.11).

^{1}H-NMR (D_2O, 400 MHz) δ 1.57-1.81 (m, 6H, CH_2), 3.42-3.85 (m, 6H, CH_2, β-CH_2), 4.97 (m, 1H, α-CH); MS (ES^+) m/z 172 $(M + H)^+$; LC-MS rt 0.4-0.5 min, m/z 172 $(M + H)^+$; UV-HPLC rt 3.60 min, 100%.

1-(S-2-Aminobutanoyl)piperidine trifluoroacetate (10.12).

^{1}H-NMR (D_2O, 400 MHz) δ 1.05 (t, 3H, CH_3), 1.63-1.77 (m, 6H, CH_2), 1.89-2.00 (m, 2H, β-CH_2), 3.50-3.68 (m, 4H, CH_2), 4.52 (t, 1H, α-CH); MS (ES^+) m/z 171 $(M + H)^+$; LC-MS rt 0.5-0.6 min, m/z 171 $(M + H)^+$; UV-HPLC rt 7.92 min, 96%.

1-(S-Norvalyl)piperidine trifluoroacetate (10.13).

^{1}H-NMR (D_2O, 400 MHz) δ 1.01 (t, 3H, CH_3), 1.41-1.51 (m, 2H, γ-CH_2), 1.59-1.78 (m, 6H, CH_2), 1.85-1.89 (m, 2H, β-CH_2), 3.50-3.68 (m, 4H, CH_2), 4.55 (t, 1H, α-CH); MS (ES^+) m/z 185 $(M + H)^+$; LC-MS rt 0.7-0.8 min, m/z 185 $(M + H)^+$; UV-HPLC rt 9.91 min, 100%.

1-(S-Norleucyl)piperidine trifluoroacetate (10.14).

^{1}H-NMR (D_2O, 400 MHz) δ 0.95 (t, 3H, CH_3), 1.30-1.42 (m, 4H, CH_2), 1.59-1.76 (m, 6H, CH_2), 1.87-1.90 (m, 2H, β-CH_2), 3.49-3.69 (m, 4H, CH_2), 4.54 (t, 1H, α-CH); MS (ES^+) m/z 199 $(M + H)^+$; LC-MS rt 0.5-0.7 min, m/z 199 $(M + H)^+$; UV-HPLC rt 11.96 min, 96%.

4-(L-2.4-diaminobutanoyl)morfoline ditrifluoroacetate (12).

^{1}H-NMR (D_2O, 400 MHz) δ 2.27-2.38 (m, 2H, β-CH_2), 3.12-3.28 (m, 2H, γ-CH_2), 3.61-3.85 (m, 8H, CH_2), 4.71 (t, 1H, α-CH); MS (ES^+) m/z 188 $(M + H)^+$.

1-(L-2.4-diaminobutanoyl)piperazine tritrifluoroacetate (13).

^{1}H-NMR (D_2O, 400 MHz) δ 2.25-2.40 (m, 2H, β-CH_2), 3.12-3.28 (m, 2H, γ-CH_2), 3.33-3.50 (m, 4H, CH_2),), 3.75-4.15 (m, 4H, CH_2) 4.76 (t, 1H, α-CH); MS (ES^+) m/z 187 $(M + H)^+$.

General procedure for synthesis of thioamides (4, 11)

The protected amino acids amides (respectively 2 and 10) were prepared by paralel synthesis using the PASP-protocol. Thioxylation of these compounds was performed according to the following procedure: To a solution of the Boc-protected amino acid amides (2 eq) in 5 ml of toluene was added 2,4-bis(*p*-methoxyphenyl)-1,3-dithiadiphosphatane 2,4-disulfide (Lawesson's reagent) (1 eq). The reaction mixture was stirred for 2 h at 80°C. The solvent was removed by evaporation and the crude compound was purified by preparative TLC (EtOAc/hexane, 40:60). Pure compounds were deprotected according to the general procedure.

Lys Ψ[CS-N]-Thia (4.1).

^{1}H-NMR (D_2O, 400 MHz) δ 1.43-1.80 (m, 4H, CH_2), 1.95-2.07 (m, 2H, CH_2), 3.04-3.34 (m, 4H, ε-CH_2, 5-CH_2), 4.00-4.28 (m, 2H, CH_2), 4.57-4.68 (m, 1H, α-CH), 4.80-5.09 (m, 2H, 2-CH2); MS (ES^+) m/z 234 $(M + H)^+$.

Cha Ψ[CS-N]-Pip (11.1).

^{1}H-NMR (D_2O, 400 MHz) δ 0.95-2.1 (m, 19H, CH_2, CH), 3.71-3.90 (m, 2H, CH_2), 4.15-4.39 (m, 2H, CH_2), 4.62-4.75 (m, 1H, α-CH); MS (ES^+) m/z 255 $(M + H)^+$.

Ile Ψ[CS-N]-Pip (11.2).

^{1}H-NMR (D_2O, 400 MHz) δ 0.95-1.08 (m, 6H, CH_3), 1.10-2.12 (m, 9H, CH_2, CH), 3.10-3.26 (m, 1H, CH_2), 3.71-3.95 (m, 2H, CH_2), 4.1-4.21 (m, 1H, CH_2), 4.42-4.50 (m, 0.5H, α-CH),4.6-4.76 (m, 0.5H, α-CH); MS (ES^+) m/z 215 $(M + H)^+$.

Dab Ψ[CS-N]-Pip (11.3).

^{1}H-NMR (D_2O, 400 MHz) δ 1.61- 1.63 (m, 6H, 3-CH_2, 4-CH_2, 5-CH_2), 2.30-2.35 (m, 2H, β-CH_2), 3.10-3.26 (m, 2H, γ-CH_2), 3.82-3.98 (m, 2H) and 4.12-4.20 (m, 1H) and 4.36-4.44 (m, 1H) (2-CH_2, 6-CH_2), 4.91 (t, 1H, α-CH); MS (ES^+) m/z 202 $(M + H)^+$.

Orn Ψ[CS-N]-Pip (11.4).

^{1}H-NMR (D_2O, 400 MHz) δ 1.82-1.99 (m, 8H, CH_2), 2.03-2.09 (m, 2H, β-CH_2), 3.12 (t, 2H, δ-CH_2), 3.89-4.03 (m, 2H, CH_2), 4.20-4.27 (m, 1H, CH_2), 4.42-4.48 (m, 1H, CH_2), 4.90 (t, 1H, α-CH); MS (ES^+) m/z 216 $(M + H)^+$.

Lys Ψ[CS-N]-Pip (11.5).

^{1}H-NMR (D_2O, 400 MHz) δ 1.43-1.62 (m, 2H) and 1.71-1.83 (m, 8H) (γ-CH_2, δ-CH_2, 3-CH_2, 4-CH_2, 5-CH_2), 1.93-2.00 (m, 2H, β-CH_2), 3.04 (t, 2H, ε-CH_2), 3.80-3.96 (m, 2H) and 4.07-4.22 (m, 1H), 4.34-4.41 (m, 1H) (2-CH_2, 6-CH_2), 4.74- 4.79 (m, 1H, α-CH); MS (ES^+) m/z 230 $(M + H)^+$.

3-Substituted pyrrolidide analogues were synthesised from 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-hydroxy-pyrrolidine.

1-(L-Lysyl)-3(R,S)-hydroxypyrrolidine trifluoroacetate (9.2).

To a mixture of N-(tert-butyloxycarbonyl)-L-lysine (1.1 eq, 2.28 g), triethylamine (3 eq, 2.53 ml) and TBTU (1.1 eq, 2.12 g) in DMF (40 ml) was added (R,S)-3-hydroxypyrrolidine (1 eq, 522 mg). After stirring at room temperature overnight, water was added and the mixture was extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with 1N HCl (2 x 25 ml), 5% $NaHCO_3$ (2 x 25 ml) and brine (25 ml). The organic layer was dried over $NaSO_4$, evaporated and purified by column chromatography yielding 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-hydroxy-pyrrolidine (87%). This Boc-protected compound was treated with a mixture of TFA/DCM (1/1, 10 ml) at room temperature. The title compound was obtained after evaporation and coevaporation with diethylether.

^{1}H-NMR (D_2O, 400 MHz) δ 1.48-1.68 (m, 2H, CH_2), 1.71-1.80 (m, 2H, CH_2), 1.93-2.25 (m, 4H, CH_2), 3.06 (br s, 2H, ε-CH_2), 3.54-3.88 (m, 4H, CH_2), 4.27-4.42 (m, 1H, α-CH), 4.57-4.66 (m, 1H, 3-CH); MS (ES^+) m/z 216 $(M + H)^+$.

1-(L-Lysyl)-3(R,S)-azidopyrrolidine trifluoroacetate (9.4).

To a solution of 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-hydroxypyrrolidine (1.5 mmol, 620 mg) in dry 1.2-dichloroethane (20 ml) was added triethylamine (4.5 mmol, 574 µl) and p-toluenesulphonyl chloride (2.5 mmol, 457 mg) at 0°C. The mixture was stirred at room temperature for 48 h (after 24 h an second addition of p-toluenesulphonyl chloride (1.5 mmol) occured). Water (30 ml) was added and the mixture was extracted with CH_2Cl_2 (2 x 80 ml). The organic layer was washed with 5% $NaHCO_3$ (2 x 50 ml), dried, evaporated and purified by column chromatography ($CHCl_3$) yielding 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-azidoyrrolidine (70%). A solution of this compound (0.95 mmol, 540 mg) in DMF (15 ml) was

treated with NaN_3 (4.75 mmol, 390 mg) and stirred at 80 °C for 5 h. EtOAc (50 ml) was added and the resulting mixture was washed with 5% $NaCO_3$ (2 x 30 ml). The organic layer was dried, evaporated and purified by column chromatography yielding a pale yellow oil. Deprotection was done according to the general procedure to yield the title compound. ^{1}H-NMR (D_2O, 400 MHz) δ 1.49-1.60 (m, 2H, CH_2), 1.72-1.82 (m, 2H, CH_2), 1.94-2.03 (m, 2H, CH_2), 2.17-2.38 (m, 2H, 4-CH_2), 3.07 (br s, 2H, ε-CH_2), 3.56-3.99 (m, 4H, CH_2), 4.30-4.42 (m, 1H, α-CH), 4.46-4.55 (m, 1H, 3-CH); MS (ES^+) m/z 241 $(M + H)^+$.

1-(L-Lysyl)-3(R,S)-benzoyloxypyrrolidine trifluoroacetate (9.6).

A solution of 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-hydroxypyrrolidine (1.16 mmol, 480 mg) in dry pyridine (15 ml) was treated with benzoyl chloride (1.28 mol, 148 µl) at 0 °C and stirred for 3 h at room temperature. After cooling the reaction mixture to 0 °C, water was added to the residue and solvents were evaporated. Dichloromethane was added to the redidue and the mixture was washed with 5% $NaHCO_3$. The organic layer was dried, evaporated and purified by preparative TLC using EtOAc as eluent to yield the pure 1-[N-(tert-butyloxycarbonyl)-L-lysyl]-3(R,S)-benzoyloxypyrrolidine as an oil (53%). Deprotection was done according to the general procedure to yield the title compound.

^{1}H-NMR (D_2O, 400 MHz) δ 1.44-1.60 (m, 2H, CH_2, 4H, CH_2), 2.31-2.52 (m, 2H, CH_2), 2.55-2.70 (m, 0.5H, ε-CH_2), 2.90 (br s, 0.5H, ε-CH_2), 3.08 (br s, 1H, ε-CH_2), 3.72-4.05 (m, 4H, CH_2), 4.34-4.46 (m, 1H, α-CH), 5.62-5.73 (m, 1H, 3-CH), 7.56-7.64 (m, 2H, m-H_{arom}), 7.72-7.81 (m, 1H, p-H_{arom}), 8.05-8.12 (m, 2H, o-H_{arom}); MS (ES^+) m/z 320 $(M + H)^+$.

General procedure for the synthesis of dipeptide nitriles (14, 15 and 16).

To a mixture of Boc-Xaa-OH (1.1 eq), triethylamine (3 eq) and TBTU (1.1 eq) in DMF was added YaaNH_2 (1 eq) (AlaNH_2 and ProNH_2 were commercially available; L-HomoProNH_2 was prepared from L-pipecolinic acid (1 eq) by reaction with N-hydroxysuccinimide (1.05 eq) and dicyclohexylcarbodiimide (DCC, 1.05 eq) in DCM (yield: 90%), followed by treatment of a solution in dioxane with ammonium gas (yield: 99%). After stirring overnight at room temperature, water was added and the mixture was extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with 1N HCl (2 x 25 ml), 5% $NaHCO_3$ (2 x 25 ml) and brine (25 ml). The organic layer was dried over $NaSO_4$, evaporated and purified by column chromatography yielding of Boc-Xaa-YaaNH_2 (86%). Dehydratation of the amide function to the nitrile was done according the following procedure: To a solution of Boc-Xaa-YaaNH_2 (1 eq) and imidazol (2 eq) in pyridine at –30 °C was slowly added phosphorusoxychloride (4 eq).

The solution was allowed to attain room temperature and the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated and the residue was extracted with 1N HCl and diethylether. The organic layer was dried, evaporated and the residue was purified by prepartive TLC to yield the Boc protected dipeptide nitrile (60%). Boc deprotection was done according to the general procedure.

2-amino-2-(L-Lysyl)propanenitrile ditrifluoroacetate (14).

^{1}H-NMR (D_2O, 400 MHz) δ 1.43-1.57 (m, 2H, CH_2), 1.61 (d, 3H, CH_3), 1.69-1.78 (m, 2H, CH_2), 1.91-2.01 (m, 2H, CH_2), 3.03 (t, 2H, ε-CH_2), 4.04 (t, 1H, α-CH), 4.79-4.89 (m, 1H, α-CH); MS (FAB^+) m/z 199 $(M + H)^+$.

1-(L-Lysyl)-2(S)-cyanopyrrolidine ditrifluoroacetate (15).

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.53 (m, 2H, CH_2), 1.72-1.77 (m, 2H, CH_2), 1.98-2.12 (m, 2H, CH_2), 2.14-2.26 (m, 2H, CH_2), 2.32-2.43 (m, 2H, CH_2), 3.02-3.06 (m, 2H, ε-CH_2), 3.70-3.74 (m, 2H, 5-CH_2), 4.37 (t, 1H, α-CH), 4.83-4.88 (m, 1H, α-CH); MS (FAB^+) m/z 225 $(M + H)^+$.

1-(L-Lysyl)-2(R,S)-cyanopiperidine ditrifluoroacetate (16.1).

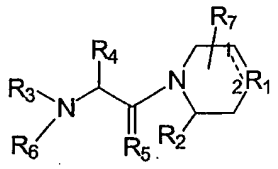
^{1}H-NMR (D_2O, 400 MHz) δ 1.42-1.63 (m, 3H, CH_2), 1.71-2.02 (m, 8H, CH_2), 2.18-2.29 (m, 1H, CH_2), 3.00-3.41 (m, 2H, 6-CH_2), 3.46-3.50 (m, 1H, ε-CH_2), 3.88-4.00 (m, 1H, ε-CH_2), 4.53-4.67 (m, 1H, α-CH), 5.69-5.88 (m, 1H, 2-CH); MS (ES^+) m/z 239 $(M + H)^+$.

1-(L-2,4-Diaminobutanoyl)-2(S)-cyanopiperidine ditrifluoroacetate (16.2).

^{1}H-NMR (D_2O, 400 MHz) δ 1.50-1.68 (m, 1H, CH_2), 1.72-2.00 (m, 4H, CH_2), 2.08-2.19 (m, 1H, CH_2), 2.35-2.49 (m, 2H, CH_2), 3.10-3.29 (m, 2H, 6-CH_2), 3.48-3.53 (m, 1H, γ-CH_2), 3.85-3.98 (m, 1H, γ-CH_2), 4.70-4.82 (m, 1H, α-CH), 5.69-5.89 (m, 1H, 2-CH_2); MS (ES^+) m/z 211 $(M + H)^+$.

Claims

1. A compound having a modulating activity on a serine type dipeptidyl peptidase and having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,



formula I

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia and imino, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3, R^4 and R^6 are selected from the group comprising hydrogen, oxyalkyl, alkyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkylamino, aminoalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, aminoalkanoyl, aminocarbonyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl,

arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^{1}oxy, Het^{1}alkyl, Het^{1}oxyalkyl, Het^{1}cycloalkyl, Het^{1}alkoxycarbonyl, Het^{1}oxycarbonyl, Het^{1}alkanoyl, Het^{1}alkyloxyalkyl, Het^{1}oxyalkylcarbonyl, Het^{1}alkyloxyalkylcarbonyl, Het^{1}aminocarbonyl, Het^{1}carbonyloxyalkyl, Het^{1}alkylcarbonyloxyalkyl, Het^{1}aryl, Het^{1}arylaminoalkoxy, Het^{1}arylamino, Het^{1}arylaminoalkyl, Het^{1}arylaminoalkylamino, Het^{1}aryloxy, Het^{1}aryloxyalkoxy, Het^{1}aryloxyalkyl, Het^{1}aryloxyalkylamino, Het^{1}aralkyl, Het^{1}aralkoxy, Het^{1}aralkylamino, Het^{1}aralkanoyl, Het^{1}aroyl, Het^{1}arylcarbonyl, Het^{1}aryloxycarbonyl, Het^{1}arylthiocarbonyl, Het^{1}aralkoxycarbonyl, Het^{1}arylalkylthiocarbonyl, Het^{1}aryloxyalkyl, Het^{1}arylthioalkyl, Het^{1}haloalkyl, Het^{1}aryloxycarbonylalkyl, Het^{1}aryloxyalkanoyl, Het^{1}aralkylcarbonyloxyalkyl, Het^{1}arylaminocarbonyl, Het^{1}aralkylaminocarbonyl, Het^{1}alkylaminoalkyl, Het^{1}aralkylaminoalkyl, Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl, Het^{1}aralkanoylaminoaryl, Het^{1}alkyloxycarbonylaminoaryl, Het^{1}aryloxycarbonylaminoaryl, Het^{1}aralkoxycarbonylaminoaryl, Het^{1}alkylaminocarbonylaminoaryl, Het^{1}arylaminocarbonylaminoaryl, Het^{1}aralkylaminocarbonylaminoaryl, Het^{1}alkylaminoaralkyl, Het^{1}arylaminoaralkyl, Het^{1}aralkylaminoaralkyl, Het^{1}alkanoylaminoaralkyl, Het^{1}aroylaminoaralkyl, Het^{1}aralkanoylaminoaralkyl, Het^{1}alkyloxycarbonylaminoaralkyl, Het^{1}aryloxycarbonylaminoaralkyl, Het^{1}aralkoxycarbonylaminoaralkyl, Het^{1}alkylaminocarbonylaminoaralkyl, Het^{1}arylaminocarbonylaminoaralkyl, Het^{1}aralkylaminocarbonylaminoaralkyl, Het^2, Het^{2}oxy, Het^{2}alkyl, Het^{2}oxyalkyl, Het^{2}cycloalkyl, Het^{2}alkoxycarbonyl, Het^{2}oxycarbonyl, Het^{2}alkanoyl, Het^{2}alkyloxyalkyl, Het^{2}oxyalkylcarbonyl, Het^{2}alkyloxyalkylcarbonyl, Het^{2}aminocarbonyl, Het^{2}carbonyloxyalkyl, Het^{2}alkylcarbonyloxyalkyl, Het^{2}aryl, Het^{2}arylaminoalkoxy, Het^{2}arylamino, Het^{2}arylaminoalkyl, Het^{2}arylaminoalkylamino, Het^{2}aryloxy, Het^{2}aryloxyalkoxy, Het^{2}aryloxyalkyl, Het^{2}aryloxyalkylamino, Het^{2}aralkyl, Het^{2}aralkoxy, Het^{2}aralkylamino, Het^{2}aralkanoyl, Het^{2}aroyl, Het^{2}arylcarbonyl, Het^{2}aryloxycarbonyl, Het^{2}arylthiocarbonyl, Het^{2}aralkoxycarbonyl,

Het^2arylalkylthiocarbonyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2haloalkyl, Het^2aryloxycarbonylalkyl, Het^2aryloxyalkanoyl, Het^2aralkylcarbonyloxyalkyl, Het^2arylaminocarbonyl, Het^2aralkylaminocarbonyl, Het^2alkylaminoalkyl, Het^2aralkylaminoalkyl, Het^2alkanoylaminoalkyl, Het^2aroylaminoalkyl, Het^2aralkanoylaminoalkyl, Het^2alkyloxycarbonylaminoalkyl, Het^2aryloxycarbonylaminoalkyl, Het^2aralkoxycarbonylaminoalkyl, Het^2alkylaminocarbonylaminoalkyl, Het^2arylaminocarbonylaminoalkyl, Het^2aralkylaminocarbonylaminoalkyl, Het^2alkylaminoaryl, Het^2arylaminoaryl, Het^2aralkylaminoaryl, Het^2alkanoylaminoaryl, Het^2aroylaminoaryl, Het^2aralkanoylaminoaryl, Het^2alkyloxycarbonylaminoaryl, Het^2aryloxycarbonylaminoaryl, Het^2aralkoxycarbonylaminoaryl, Het^2alkylaminocarbonylaminoaryl, Het^2arylaminocarbonylaminoaryl, Het^2aralkylaminocarbonylaminoaryl, Het^2alkylaminoaralkyl, Het^2arylaminoaralkyl, Het^2aralkylaminoaralkyl, Het^2alkanoylaminoaralkyl, Het^2aroylaminoaralkyl, Het^2aralkanoylaminoaralkyl, Het^2alkyloxycarbonylaminoaralkyl, Het^2aryloxycarbonylaminoaralkyl, Het^2aralkoxycarbonylaminoaralkyl, Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

wherein R^3, R^4 and R^6 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, and

wherein R^7 is selected from the group comprising hydrogen, alkyl and halogen.

2. Compound according to claim 1, having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia and imino, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, cycloalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl,

aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^{1}oxy, Het^{1}alkyl, Het^{1}oxyalkyl, Het^{1}cycloalkyl, Het^{1}alkoxycarbonyl, Het^{1}oxycarbonyl, Het^{1}alkanoyl, Het^{1}alkyloxyalkyl, Het^{1}oxyalkylcarbonyl, Het^{1}alkyloxyalkylcarbonyl, Het^{1}aminocarbonyl, Het^{1}carbonyloxyalkyl, Het^{1}alkylcarbonyloxyalkyl, Het^{1}aryl, Het^{1}arylaminoalkoxy, Het^{1}arylamino, Het^{1}arylaminoalkyl, Het^{1}arylaminoalkylamino, Het^{1}aryloxy, Het^{1}aryloxyalkoxy, Het^{1}aryloxyalkyl, Het^{1}aryloxyalkylamino, Het^{1}aralkyl, Het^{1}aralkoxy, Het^{1}aralkylamino, Het^{1}aralkanoyl, Het^{1}aroyl, Het^{1}arylcarbonyl, Het^{1}aryloxycarbonyl, Het^{1}arylthiocarbonyl, Het^{1}aralkoxycarbonyl, Het^{1}arylalkylthiocarbonyl, Het^{1}aryloxyalkyl, Het^{1}arylthioalkyl, Het^{1}haloalkyl, Het^{1}aryloxycarbonylalkyl, Het^{1}aryloxyalkanoyl, Het^{1}aralkylcarbonyloxyalkyl, Het^{1}arylaminocarbonyl, Het^{1}aralkylaminocarbonyl, Het^{1}alkylaminoalkyl, Het^{1}aralkylaminoalkyl, Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl, Het^{1}aralkanoylaminoaryl, Het^{1}alkyloxycarbonylaminoaryl, Het^{1}aryloxycarbonylaminoaryl, Het^{1}aralkoxycarbonylaminoaryl, Het^{1}alkylaminocarbonylaminoaryl, Het^{1}arylaminocarbonylaminoaryl, Het^{1}aralkylaminocarbonylaminoaryl, Het^{1}alkylaminoaralkyl, Het^{1}arylaminoaralkyl, Het^{1}aralkylaminoaralkyl, Het^{1}alkanoylaminoaralkyl, Het^{1}aroylaminoaralkyl, Het^{1}aralkanoylaminoaralkyl, Het^{1}alkyloxycarbonylaminoaralkyl,

Het^1aryloxycarbonylaminoaralkyl, Het^1aralkoxycarbonylaminoaralkyl, Het^1alkylaminocarbonylaminoaralkyl, Het^1arylaminocarbonylaminoaralkyl, Het^1aralkylaminocarbonylaminoaralkyl, Het^2, Het^2oxy, Het^2alkyl, Het^2oxyalkyl, Het^2cycloalkyl, Het^2alkoxycarbonyl, Het^2oxycarbonyl, Het^2alkanoyl, Het^2alkyloxyalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aminocarbonyl, Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aryl, Het^2arylaminoalkoxy, Het^2arylamino, Het^2arylaminoalkyl, Het^2arylaminoalkylamino, Het^2aryloxy, Het^2aryloxyalkoxy, Het^2aryloxyalkyl, Het^2aryloxyalkylamino, Het^2aralkyl, Het^2aralkoxy, Het^2aralkylamino, Het^2aralkanoyl, Het^2aroyl, Het^2arylcarbonyl, Het^2aryloxycarbonyl, Het^2arylthiocarbonyl, Het^2aralkoxycarbonyl, Het^2arylalkylthiocarbonyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2haloalkyl, Het^2aryloxycarbonylalkyl, Het^2aryloxyalkanoyl, Het^2aralkylcarbonyloxyalkyl, Het^2arylaminocarbonyl, Het^2aralkylaminocarbonyl, Het^2alkylaminoalkyl, Het^2aralkylaminoalkyl, Het^2alkanoylaminoalkyl, Het^2aroylaminoalkyl, Het^2aralkanoylaminoalkyl, Het^2alkyloxycarbonylaminoalkyl, Het^2aryloxycarbonylaminoalkyl, Het^2aralkoxycarbonylaminoalkyl, Het^2alkylaminocarbonylaminoalkyl, Het^2arylaminocarbonylaminoalkyl, Het^2aralkylaminocarbonylaminoalkyl, Het^2alkylaminoaryl, Het^2arylaminoaryl, Het^2aralkylaminoaryl, Het^2alkanoylaminoaryl, Het^2aroylaminoaryl, Het^2aralkanoylaminoaryl, Het^2alkyloxycarbonylaminoaryl, Het^2aryloxycarbonylaminoaryl, Het^2aralkoxycarbonylaminoaryl, Het^2alkylaminocarbonylaminoaryl, Het^2arylaminocarbonylaminoaryl, Het^2aralkylaminocarbonylaminoaryl, Het^2alkylaminoaralkyl, Het^2arylaminoaralkyl, Het^2aralkylaminoaralkyl, Het^2alkanoylaminoaralkyl, Het^2aroylaminoaralkyl, Het^2aralkanoylaminoaralkyl, Het^2alkyloxycarbonylaminoaralkyl, Het^2aryloxycarbonylaminoaralkyl, Het^2aralkoxycarbonylaminoaralkyl, Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio,

wherein R^6 is hydrogen, and

wherein R^7 is selected from the group comprising hydrogen, alkyl and halogen

3. Compound according to claim 1 or 2 having the general formula I, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, and thia, or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen, alkyl or cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, cycloalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^1oxy, Het^1alkyl, Het^1oxyalkyl, Het^1cycloalkyl, Het^1alkoxycarbonyl, Het^1oxycarbonyl, Het^1alkanoyl, Het^1alkyloxyalkyl, Het^1oxyalkylcarbonyl, Het^1alkyloxyalkylcarbonyl, Het^1aminocarbonyl, Het^1carbonyloxyalkyl, Het^1alkylcarbonyloxyalkyl, Het^1aryl, Het^1arylaminoalkoxy, Het^1arylamino, Het^1arylaminoalkyl, Het^1arylaminoalkylamino, Het^1aryloxy, Het^1aryloxyalkoxy, Het^1aryloxyalkyl, Het^1aryloxyalkylamino, Het^1aralkyl, Het^1aralkoxy, Het^1aralkylamino, Het^1aralkanoyl, Het^1aroyl, Het^1arylcarbonyl, Het^1aryloxycarbonyl, Het^1arylthiocarbonyl, Het^1aralkoxycarbonyl, Het^1arylalkylthiocarbonyl, Het^1aryloxyalkyl, Het^1arylthioalkyl, Het^1haloalkyl, Het^1aryloxycarbonylalkyl, Het^1aryloxyalkanoyl, Het^1aralkylcarbonyloxyalkyl, Het^1arylaminocarbonyl, Het^1aralkylaminocarbonyl, Het^1alkylaminoalkyl, Het^1aralkylaminoalkyl,

Het^1alkanoylaminoalkyl, Het^1aroylaminoalkyl, Het^1aralkanoylaminoalkyl, Het^1alkyloxycarbonylaminoalkyl, Het^1aryloxycarbonylaminoalkyl, Het^1aralkoxycarbonylaminoalkyl, Het^1alkylaminocarbonylaminoalkyl, Het^1arylaminocarbonylaminoalkyl, Het^1aralkylaminocarbonylaminoalkyl, Het^1alkylaminoaryl, Het^1arylaminoaryl, Het^1aralkylaminoaryl, Het^1alkanoylaminoaryl, Het^1aroylaminoaryl, Het^1aralkanoylaminoaryl, Het^1alkyloxycarbonylaminoaryl, Het^1aryloxycarbonylaminoaryl, Het^1aralkoxycarbonylaminoaryl, Het^1alkylaminocarbonylaminoaryl, Het^1arylaminocarbonylaminoaryl, Het^1aralkylaminocarbonylaminoaryl, Het^1alkylaminoaralkyl, Het^1arylaminoaralkyl, Het^1aralkylaminoaralkyl, Het^1alkanoylaminoaralkyl, Het^1aroylaminoaralkyl, Het^1aralkanoylaminoaralkyl, Het^1alkyloxycarbonylaminoaralkyl, Het^1aryloxycarbonylaminoaralkyl, Het^1aralkoxycarbonylaminoaralkyl, Het^1alkylaminocarbonylaminoaralkyl, Het^1arylaminocarbonylaminoaralkyl, Het^1aralkylaminocarbonylaminoaralkyl, Het^2, Het^2oxy, Het^2alkyl, Het^2oxyalkyl, Het^2cycloalkyl, Het^2alkoxycarbonyl, Het^2oxycarbonyl, Het^2alkanoyl, Het^2alkyloxyalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aminocarbonyl, Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aryl, Het^2arylaminoalkoxy, Het^2arylamino, Het^2arylaminoalkyl, Het^2arylaminoalkylamino, Het^2aryloxy, Het^2aryloxyalkoxy, Het^2aryloxyalkyl, Het^2aryloxyalkylamino, Het^2aralkyl, Het^2aralkoxy, Het^2aralkylamino, Het^2aralkanoyl, Het^2aroyl, Het^2arylcarbonyl, Het^2aryloxycarbonyl, Het^2arylthiocarbonyl, Het^2aralkoxycarbonyl, Het^2arylalkylthiocarbonyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2haloalkyl, Het^2aryloxycarbonylalkyl, Het^2aryloxyalkanoyl, Het^2aralkylcarbonyloxyalkyl, Het^2arylaminocarbonyl, Het^2aralkylaminocarbonyl, Het^2alkylaminoalkyl, Het^2aralkylaminoalkyl, Het^2alkanoylaminoalkyl, Het^2aroylaminoalkyl, Het^2aralkanoylaminoalkyl, Het^2alkyloxycarbonylaminoalkyl, Het^2aryloxycarbonylaminoalkyl, Het^2aralkoxycarbonylaminoalkyl, Het^2alkylaminocarbonylaminoalkyl, Het^2arylaminocarbonylaminoalkyl, Het^2aralkylaminocarbonylaminoalkyl, Het^2alkylaminoaryl, Het^2arylaminoaryl, Het^2aralkylaminoaryl, Het^2alkanoylaminoaryl, Het^2aroylaminoaryl, Het^2aralkanoylaminoaryl, Het^2alkyloxycarbonylaminoaryl, Het^2aryloxycarbonylaminoaryl, Het^2aralkoxycarbonylaminoaryl, Het^2alkylaminocarbonylaminoaryl, Het^2arylaminocarbonylaminoaryl, Het^2aralkylaminocarbonylaminoaryl, Het^2alkylaminoaralkyl, Het^2arylaminoaralkyl, Het^2aralkylaminoaralkyl, Het^2alkanoylaminoaralkyl, Het^2aroylaminoaralkyl, Het^2aralkanoylaminoaralkyl, Het^2alkyloxycarbonylaminoaralkyl, Het^2aryloxycarbonylaminoaralkyl, Het^2aralkoxycarbonylaminoaralkyl,

Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen, fluor or methyl.

4. Compound according to any of claims 1 to 3, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, and thia or wherein R^1 participates to a double bond between the carbon atoms in position 1 and 2,

wherein R^2 is selected from the group comprising hydrogen and cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, aryl, cycloalkyl, aralkyl, cycloalkylalkyl, alkylamino, aminoalkyl, aminoalkanoyl, aminocarbonyl, alkylaminocarbonyl, alkylaminoalkyl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxyalkylamino, aralkylamino, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyol, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl,

arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen, fluor or methyl.

5. Compound according to any of claims 1 to 4, or pharmaceutically acceptable salts, solvates or functional derivatives thereof.

wherein R^1 is selected from the group comprising $-CH_2-$, oxa, thia

wherein R^2 is selected from the group comprising hydrogen and cyano,

wherein R^3 and R^4 are selected from the group comprising hydrogen, alkyl, aryl, cycloalkyl, aralkyl, cycloalkylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, aralkylamino, aralkylaminoalkyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl

and wherein R^3 and R^4 are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2;

wherein R^5 is oxo or thio, wherein R^6 is hydrogen, and wherein R^7 is hydrogen or fluor.

6. Compound according to claim 1, being N^1-benzyl-4-oxo-4-(1-piperidinyl)-1,3(S)-butanediamine as indicated with formula IV according to the specification.

7.Compound according to claim 1, being 4-Oxo-4-(1-piperidinyl)-1,3(S)-butanediamine as indicated with formula V according to the specification.

8. Compound according to claim 1, being 4-Oxo-4-(1-piperidinyl)-1,3(R)-butanediamine as indicated with formula VI according to the specification.

9. Compound according to claim 1, being 4-(4-morpholinyl)-4-oxo-1,3(*S*)-butanediamine as indicated with formula VII according to the specification.

10. Compound according to claim 1, being 4-oxo-4-(1-piperazinyl)-1,3(*S*)-butanediamine as indicated with formula VIII according to the specification.

11. Compound according to claim 1, being benzyl 3-amino-1(S)-(1-piperidinylcarbonyl)propylcarbamate as indicated with formula IX according to the specification.

12. Compound according to claim 1, being benzyl 3-amino-4-oxo-4-(1piperidinyl)butylcarbamate as indicated with formula X according to the specification.

13. Compound according to claim 1, being N^1-benzyl-2(S)-(1-piperidinylcarbonyl)-1,4-butanediamine as indicated with formula XI according to the specification.

14. Compound according to claim 1, being *N*-[3(*S*)-amino-4-oxo-4-(1-piperidinyl)butyl]acetamide as indicated with formula XII according to the specification.

15. Compound according to claim 1, being 4-Oxo-4-(1-piperidinyl)-N^1-(4-piperidinyl)-1,3(*S*)-butanediamine as indicated with formula XIII according to the specification.

16. Compound according to claim 1, being benzyl 4-{[4-amino-2(*S*)-(1-piperidinylcarbonyl)butyl]amino}-1-piperidinecarboxylate as indicated with formula XIV according to the specification.

17. Compound according to claim 1, being *N*-[3(*S*)-amino-4-oxo-4-(1-piperidinyl)butyl]guanidine as indicated with formula XV according to the specification.

18. Compound according to claim 1, being *N*-[3-amino-1(*S*)-(1-piperidinylcarbonyl)propyl]guanidine as indicated with formula XVI according to the specification.

19. Compound according to claim 1, being *N*-(2-oxo-2-piperidin-1-ylethyl)piperidin-4-amine as indicated with formula XVII according to the specification.

20. Compound according to claim 1, being Benzyl 4{[2-oxo-2-(1-piperidinyl)ethyl]amino}-1-piperidinecarboxylate as indicated with formula XVIII according to the specification.

21. Compound according to claim 1, being *N*-[2-oxo-2-(1-piperidinyl)ethyl]cyclopentanamine as indicated with as indicated with formula XIX according to the specification.

22. Compound according to claim 1, being 1-Benzyl-*N*-[2-oxo-2-(1-piperidinyl)ethyl]-4-piperidinamine as indicated with formula XX according to the specification.

23. Compound according to claim 1, being 4-oxo-4-(1-piperidinyl)-N^3-(4-piperidinyl)-1,3(S)-butanediamine (XXI) as indicated with formula XXI according to the specification.

24. Compound according to claim 1, being 6-oxo-6-(1-piperidinyl)-1,5(*S*)-hexanediamine as indicated with formula XXII according to the specification.

25. Compound according to claim 1, being benzyl 5(*S*)-amino-6-oxo-6-(1-piperidinyl)hexylcarbamate as indicated with formula XXIII according to the specification.

26. Compound according to claim 1, being 5-oxo-5-(1-piperidinyl)-1,4(*S*)-pentanediamine as indicated with formula XXIV according to the specification.

27. Compound according to claim 1, being 3-oxo-3-(1-piperidinyl)-1,2(*S*)-propanediamine as indicated with formula XXV according to the specification.

28. Compound according to claim 1, being 3-(1*H*-imidazol-4-yl)-1-oxo-1-(1-piperidinyl)-2(*S*)-propanamine as indicated with formula XXVI according to the specification.

29. Compound according to claim 1, being 3-cyclohexyl-1-oxo-1-(1-piperidinyl)-2(*S*)-propanamine as indicated with formula XXVII according to the specification.

30. Compound according to claim 1, being 3-methyl-1-oxo-1-(1-piperidinyl)-2(*S*)-pentanamine as indicated with formula XXVIII according to the specification.

31. Compound according to claim 1, being 2(*S*)-amino-3-oxo-3-(1-piperidinyl)-1-propanol as indicated with formula XXIX according to the specification.

32. Compound according to claim 1, being 1-oxo-1-(1-piperidinyl)-2(*S*)-butanamine as indicated with formula XXX according to the specification.

33. Compound according to claim 1, being 1-oxo-1-(1-piperidinyl)-2(*S*)-pentanamine as indicated with formula XXXI according to the specification.

34. Compound according to claim 1, being 1-oxo-1-(1-piperidinyl)-2(*S*)-hexanamine as indicated with formula XXXII according to the specification.

35. Compound according to claim 1, being 6-(3,6-dihydro-1(2*H*)-pyridinyl)-6-oxo-1,5(*S*)-hexanediamine as indicated with formula XXXIII according to the specification.

36. Compound according to claim 1, being *N*-[4(*S*)-amino-5-oxo-5-(1-piperidinyl)pentyl]guanidine as indicated with formula XXXIV according to the specification.

37. Compound according to claim 1, being 1-(*S*-2,6-Diaminohexanoyl)-2(*R,S*)-piperidinecarbonitrile as indicated with formula XXXV according to the specification.

38. Compound according to claim 1, being 1-(*S*-2,4-diaminobutanoyl)-2(*S*)-piperidinecarbonitrile as indicated with formula XXXVI according to the specification.

39. Compound according to claim 1, being 3-cyclohexyl-1-(1-piperidinyl)-1-thioxo-2(*S*)-propanamine as indicated with formula XXXVII according to the specification.

40. Compound according to claim 1, being 2(*S*)-methyl-1-(1-piperidinylcarbothioyl)butylamine as indicated with formula XXXVIII according to the specification.

41. Compound according to claim 1, being 4-(1-piperidinyl)-4-thioxo-1,3(*S*)-butanediamine as indicated with formula XXXIX according to the specification.

42. Compound according to claim 1, being 5-(1-piperidinyl)-5-thioxo-1,4(*S*)-pentanediamine as indicated with formula XXXX according to the specification.

43. Compound according to claim 1, being 6-(1-piperidinyl)-6-thioxo-1,5(*S*)-hexanediamine as indicated with formula XXXXI according to the specification.

44. Compound according to claim 1, being *N*-cyclohexyl-2-oxo-2-(1-piperidinyl)-ethaneamine as indicated with formula XXXXII according to the specification.

45. Compound according to claim 1, being *N*-benzyl-2-oxo-2-(1-piperidinyl)-ethaneamine as indicated with formula XXXXIII according to the specification.

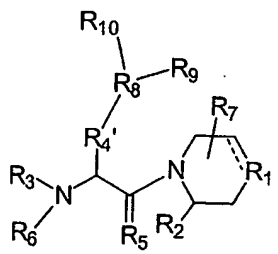
46. Compound according to claim 1, being as indicated with *N*-piperonyl-2-oxo-2-(1-piperidinyl)-ethaneamine formula XXXXIV according to the specification.

47. Compound according to claim 1, being *N*-cyclohexyl-2-thioxo-2-(1-piperidinyl)-ethaneamine as indicated with formula XXXXV according to the specification.

48. Compound according to claim 1, being *N*-benzyl-2-thioxo-2-(1-piperidinyl)-ethaneamine as indicated with formula XXXXVI according to the specification.

49. Compound according to claim 1, being *N*-piperonyl-2-thioxo-2-(1-piperidinyl)-ethaneamine as indicated with formula XXXXVII according to the specification.

50. Compound having general formula II, or pharmaceutically acceptable salts, solvates or functional derivatives thereof,



formula II

wherein R_1, R_2, R_3, R_5, R_6, R_7 have the same meaning as indicated claim 1,

wherein $R_{4'}$, R_8, R_9, R_{10} are selected from the group comprising nitrogen, hydrogen, oxyalkyl, alkyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkylamino, aminoalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, aminoalkanoyl, aminocarbonyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, alkylaminocarbonyl, alkylaminoalkyl, aryl, arylaminoalkoxy, arylamino, aminoaryl, aminoaralkyl, arylaminoalkyl, arylaminoalkylamino, aryloxy, aryloxyalkoxy, aryloxyalkyl, aryloxyalkylamino, aralkyl, aralkoxy, aralkylamino, aralkanoyl, aroyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalkyl, arylthioalkyl, haloalkyl, aryloxycarbonylalkyl, aryloxyalkanoyl, aralkylcarbonyloxyalkyl, arylaminocarbonyl, aralkylaminocarbonyl, aralkylaminoalkyl, alkanoylaminoalkyl, aroylaminoalkyl, aralkanoylaminoalkyl, alkyloxycarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aralkoxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, arylaminocarbonylaminoalkyl, aralkylaminocarbonylaminoalkyl, alkylaminoaryl, arylaminoaryl, aralkylaminoaryl, alkanoylaminoaryl, aroylaminoaryl, aralkanoylaminoaryl, alkyloxycarbonylaminoaryl, aryloxycarbonylaminoaryl, aralkoxycarbonylaminoaryl, alkylaminocarbonylaminoaryl, arylaminocarbonylaminoaryl, aralkylaminocarbonylaminoaryl, alkylaminoaralkyl, arylaminoaralkyl, aralkylaminoaralkyl, alkanoylaminoaralkyl, aroylaminoaralkyl, aralkanoylaminoaralkyl, alkyloxycarbonylaminoaralkyl, aryloxycarbonylaminoaralkyl, aralkoxycarbonylaminoaralkyl, alkylaminocarbonylaminoaralkyl, arylaminocarbonylaminoaralkyl, aralkylaminocarbonylaminoaralkyl, carboxyl piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, guanidinoalkyl, amidinoalkyl, Het^1, Het^1oxy, Het^1alkyl, Het^1oxyalkyl, Het^1cycloalkyl, Het^1alkoxycarbonyl, Het^1oxycarbonyl, Het^1alkanoyl, Het^1alkyloxyalkyl, Het^1oxyalkylcarbonyl, Het^1alkyloxyalkylcarbonyl, Het^1aminocarbonyl, Het^1carbonyloxyalkyl, Het^1alkylcarbonyloxyalkyl, Het^1aryl, Het^1arylaminoalkoxy, Het^1arylamino, Het^1arylaminoalkyl, Het^1arylaminoalkylamino, Het^1aryloxy, Het^1aryloxyalkoxy, Het^1aryloxyalkyl, Het^1aryloxyalkylamino, Het^1aralkyl, Het^1aralkoxy, Het^1aralkylamino, Het^1aralkanoyl, Het^1aroyl, Het^1arylcarbonyl, Het^1aryloxycarbonyl, Het^1arylthiocarbonyl, Het^1aralkoxycarbonyl, Het^1arylalkylthiocarbonyl, Het^1aryloxyalkyl, Het^1arylthioalkyl, Het^1haloalkyl, Het^1aryloxycarbonylalkyl, Het^1aryloxyalkanoyl, Het^1aralkylcarbonyloxyalkyl, Het^1arylaminocarbonyl, Het^1aralkylaminocarbonyl, Het^1alkylaminoalkyl, Het^1aralkylaminoalkyl,

Het^{1}alkanoylaminoalkyl, Het^{1}aroylaminoalkyl, Het^{1}aralkanoylaminoalkyl, Het^{1}alkyloxycarbonylaminoalkyl, Het^{1}aryloxycarbonylaminoalkyl, Het^{1}aralkoxycarbonylaminoalkyl, Het^{1}alkylaminocarbonylaminoalkyl, Het^{1}arylaminocarbonylaminoalkyl, Het^{1}aralkylaminocarbonylaminoalkyl, Het^{1}alkylaminoaryl, Het^{1}arylaminoaryl, Het^{1}aralkylaminoaryl, Het^{1}alkanoylaminoaryl, Het^{1}aroylaminoaryl, Het^{1}aralkanoylaminoaryl, Het^{1}alkyloxycarbonylaminoaryl, Het^{1}aryloxycarbonylaminoaryl, Het^{1}aralkoxycarbonylaminoaryl, Het^{1}alkylaminocarbonylaminoaryl, Het^{1}arylaminocarbonylaminoaryl, Het^{1}aralkylaminocarbonylaminoaryl, Het^{1}alkylaminoaralkyl, Het^{1}arylaminoaralkyl, Het^{1}aralkylaminoaralkyl, Het^{1}alkanoylaminoaralkyl, Het^{1}aroylaminoaralkyl, Het^{1}aralkanoylaminoaralkyl, Het^{1}alkyloxycarbonylaminoaralkyl, Het^{1}aryloxycarbonylaminoaralkyl, Het^{1}aralkoxycarbonylaminoaralkyl, Het^{1}alkylaminocarbonylaminoaralkyl, Het^{1}arylaminocarbonylaminoaralkyl, Het^{1}aralkylaminocarbonylaminoaralkyl, Het^2, Het^{2}oxy, Het^{2}alkyl, Het^{2}oxyalkyl, Het^{2}cycloalkyl, Het^{2}alkoxycarbonyl, Het^{2}oxycarbonyl, Het^{2}alkanoyl, Het^{2}alkyloxyalkyl, Het^{2}oxyalkylcarbonyl, Het^{2}alkyloxyalkylcarbonyl, Het^{2}aminocarbonyl, Het^{2}carbonyloxyalkyl, Het^{2}alkylcarbonyloxyalkyl, Het^{2}aryl, Het^{2}arylaminoalkoxy, Het^{2}arylamino, Het^{2}arylaminoalkyl, Het^{2}arylaminoalkylamino, Het^{2}aryloxy, Het^{2}aryloxyalkoxy, Het^{2}aryloxyalkyl, Het^{2}aryloxyalkylamino, Het^{2}aralkyl, Het^{2}aralkoxy, Het^{2}aralkylamino, Het^{2}aralkanoyl, Het^{2}aroyl, Het^{2}arylcarbonyl, Het^{2}aryloxycarbonyl, Het^{2}arylthiocarbonyl, Het^{2}aralkoxycarbonyl, Het^{2}arylalkylthiocarbonyl, Het^{2}aryloxyalkyl, Het^{2}arylthioalkyl, Het^{2}haloalkyl, Het^{2}aryloxycarbonylalkyl, Het^{2}aryloxyalkanoyl, Het^{2}aralkylcarbonyloxyalkyl, Het^{2}arylaminocarbonyl, Het^{2}aralkylaminocarbonyl, Het^{2}alkylaminoalkyl, Het^{2}aralkylaminoalkyl, Het^{2}alkanoylaminoalkyl, Het^{2}aroylaminoalkyl, Het^{2}aralkanoylaminoalkyl, Het^{2}alkyloxycarbonylaminoalkyl, Het^{2}aryloxycarbonylaminoalkyl, Het^{2}aralkoxycarbonylaminoalkyl, Het^{2}alkylaminocarbonylaminoalkyl, Het^{2}arylaminocarbonylaminoalkyl, Het^{2}aralkylaminocarbonylaminoalkyl, Het^{2}alkylaminoaryl, Het^{2}arylaminoaryl, Het^{2}aralkylaminoaryl, Het^{2}alkanoylaminoaryl, Het^{2}aroylaminoaryl, Het^{2}aralkanoylaminoaryl, Het^{2}alkyloxycarbonylaminoaryl, Het^{2}aryloxycarbonylaminoaryl, Het^{2}aralkoxycarbonylaminoaryl, Het^{2}alkylaminocarbonylaminoaryl, Het^{2}arylaminocarbonylaminoaryl, Het^{2}aralkylaminocarbonylaminoaryl, Het^{2}alkylaminoaralkyl, Het^{2}arylaminoaralkyl, Het^{2}aralkylaminoaralkyl, Het^{2}alkanoylaminoaralkyl, Het^{2}aroylaminoaralkyl, Het^{2}aralkanoylaminoaralkyl, Het^{2}alkyloxycarbonylaminoaralkyl, Het^{2}aryloxycarbonylaminoaralkyl, Het^{2}aralkoxycarbonylaminoaralkyl,

Het^2alkylaminocarbonylaminoaralkyl, Het^2arylaminocarbonylaminoaralkyl, Het^2aralkylaminocarbonylaminoaralkyl,

and wherein R_4, R_8, R_9, R_{10} are optionally substituted by one or more substituents independently selected from the group comprising hydrogen, amino, hydroxy, halogen, alkyl, alkylamino, alkanoyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, aminoaryl, arylaminoalkyl, arylaminoalkylamino, aralkanoyl, aroyl, piperazinyl, piperidinyl, pyrrolidinyl, immidazolidinyl, morpholinyl, amidino, acetyl, Het^1 and Het^2.

51. Compounds of the invention having general formula II as represented in Table A.

52. Compound according to any of claims 1 to 51 for use as a medicament.

53. Compound according to any of claims 1 to 51 for use in the treatment of diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase.

54. Compound according to any of claims 1 to 51 for use in the treatment of diseases associated with excessive, impaired or unbalanced activity of DPPIV.

55. Compound according to any of claims 1 to 51 for use in the treatment of diseases associated with excessive, impaired or unbalanced activity of DPPII.

56. Compound according to any of claims 1 to 51 for use in diagnostic and research methods such as fluorescence, purification and radio-assays, imaging, *in situ* histochemical and cytochemical staining.

57. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for inhibiting the activity of a serine type dipeptidyl peptidase.

58. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for inhibiting the activity of DPPIV.

59. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for inhibiting the activity of DPPII.

60. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of a serine type dipeptidyl peptidase.

61. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of DPPIV.

62. Use of a compound according to any of claims 1 to 51 in the preparation of a medicament for treating diseases associated with excessive, impaired or unbalanced activity of DPPII.

63. Pharmaceutical composition comprising a therapeutically effective amount of one or more compounds according to any of claims 1 to 51, and a pharmaceutically acceptable excipient.

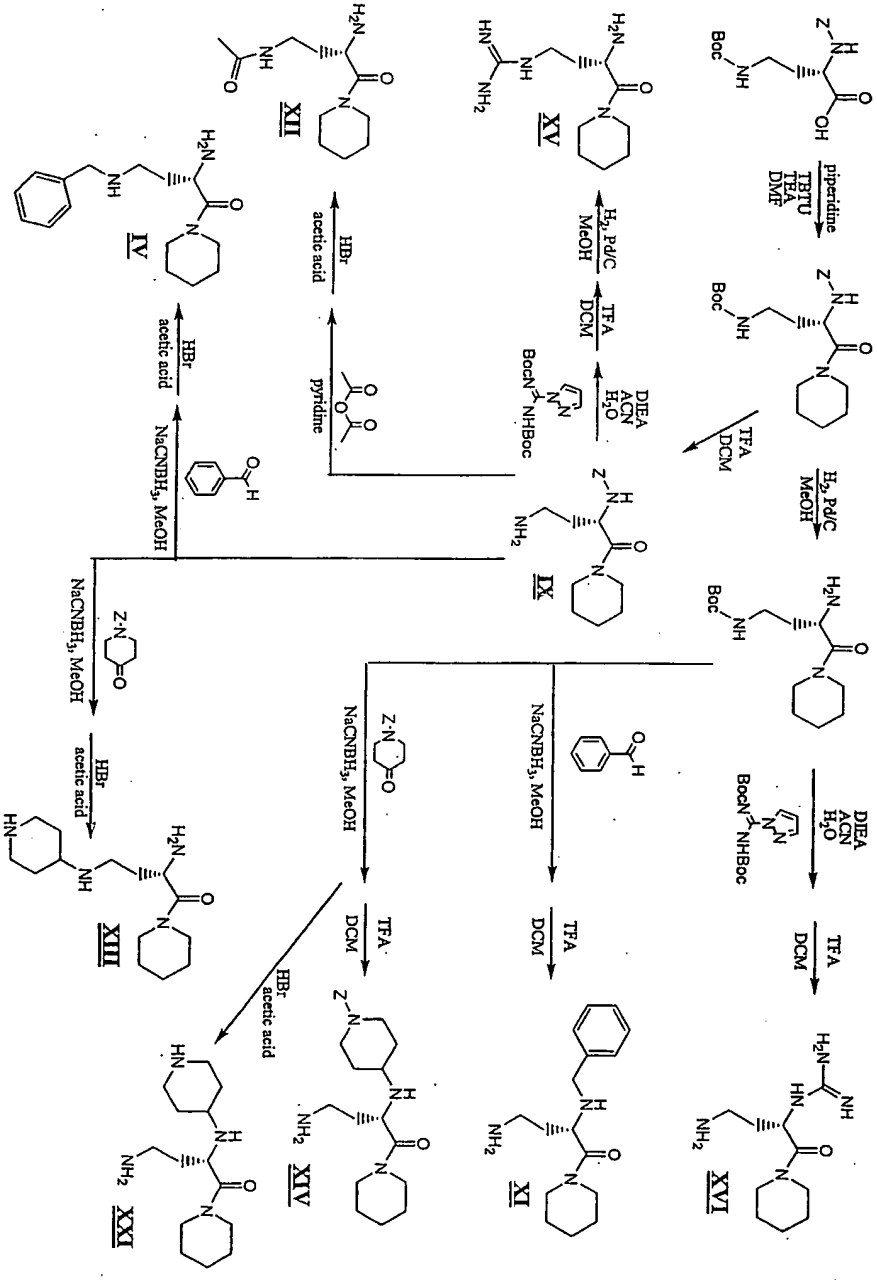

piperidine
TBTU
TEA
DMF
TFA
DCM
H2, Pd/C
MeOH
DIEA
ACN
H2O
NaCNBH3, MeOH
HBr
acetic acid
pyridine
XVI
XI
XIV
XXI
XIII
IX
XV
XII
IV

Fig. 1

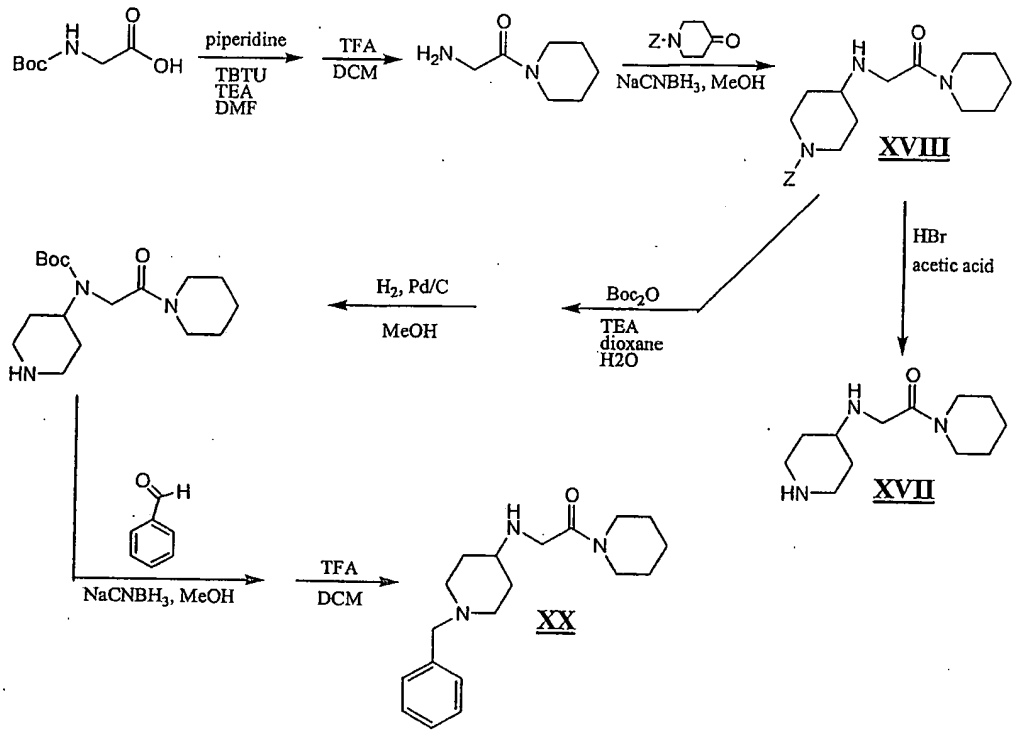
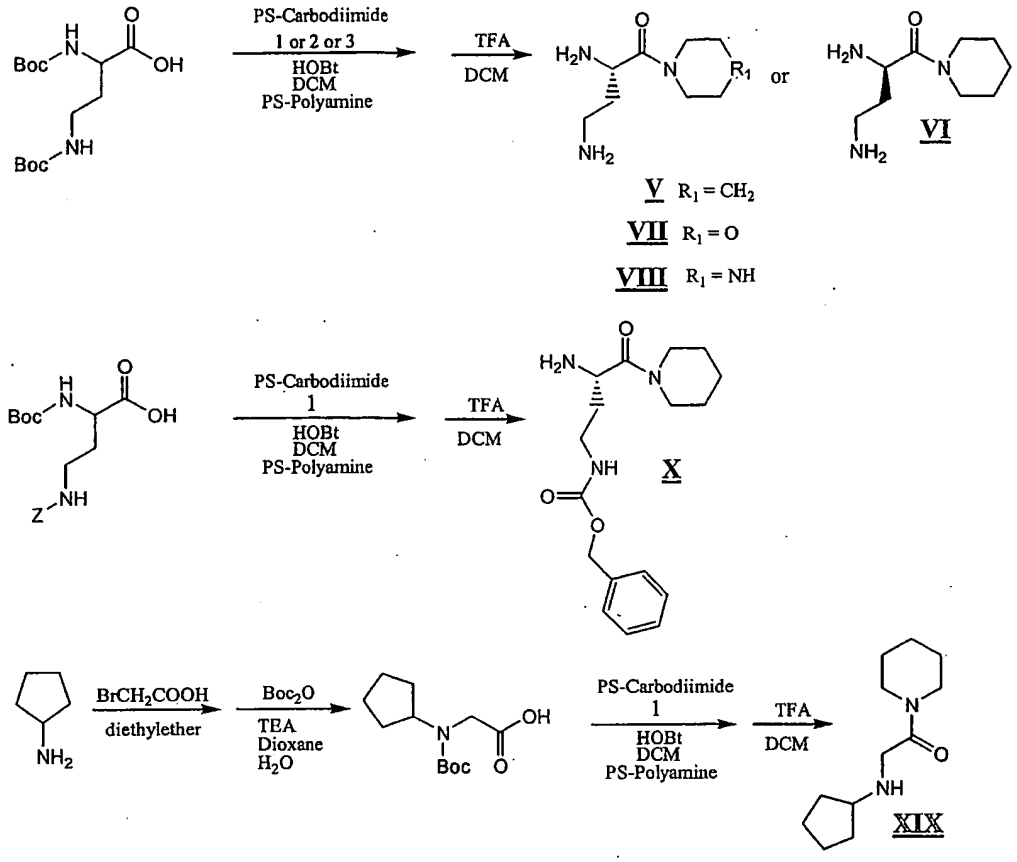

Boc
OH
piperidine
TBTU
TEA
DMF
TFA
DCM
H2N
Z·N
NaCNBH3, MeOH
XVIII
Z
HBr
acetic acid
XVII
HN
Boc2O
TEA
dioxane
H2O
H2, Pd/C
MeOH
NaCNBH3, MeOH
TFA
DCM
XX

Fig. 2



1) piperidine 2) morfoline 3) Boc-piperazine

Fig. 3

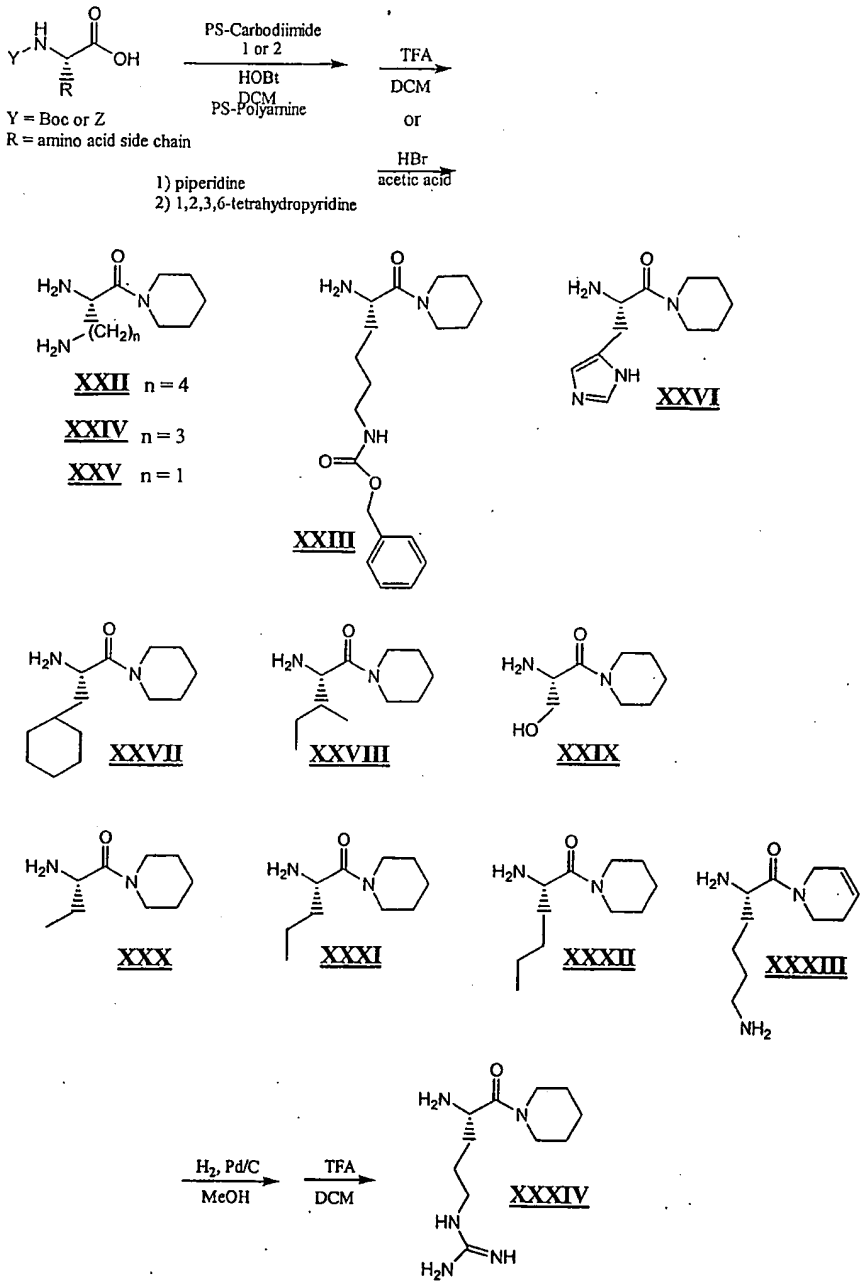

PS-Carbodiimide
1 or 2
HOBt
DCM
PS-Polyamine
TFA
DCM
or
HBr
acetic acid
Y = Boc or Z
R = amino acid side chain
1) piperidine
2) 1,2,3,6-tetrahydropyridine
XXII n = 4
XXIV n = 3
XXV n = 1
XXIII
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI
XXXII
XXXIII
H2, Pd/C
MeOH
TFA
DCM
XXXIV

Fig. 4

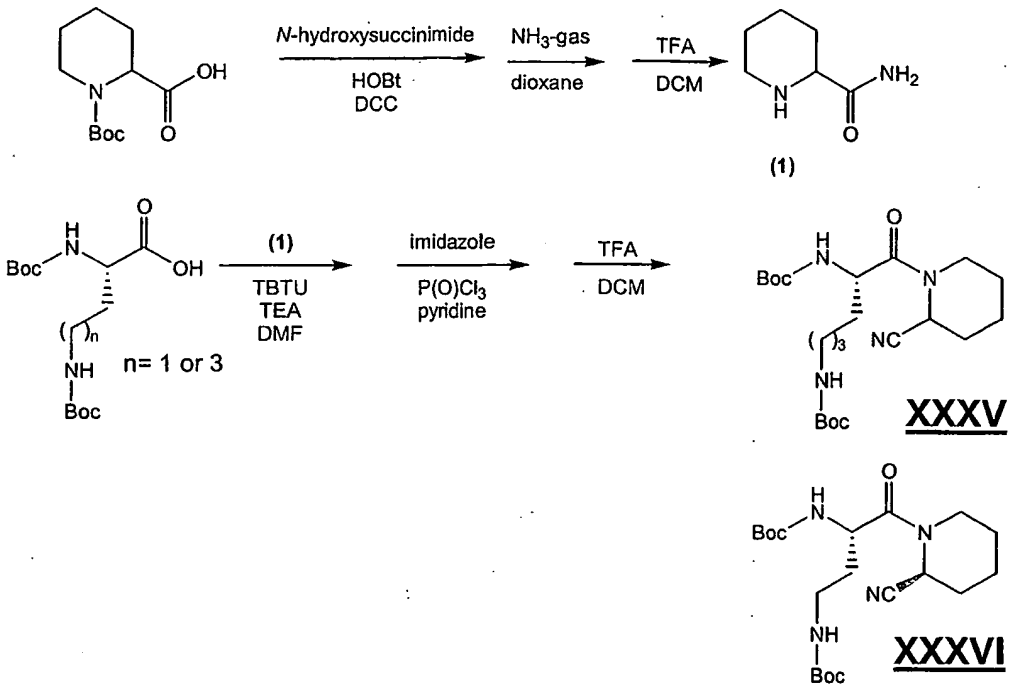

N-hydroxysuccinimide
HOBt
DCC
NH3-gas
dioxane
TFA
DCM
OH
Boc
NH2
(1)
Boc
OH
n= 1 or 3
(1)
TBTU
TEA
DMF
imidazole
P(O)Cl3
pyridine
TFA
DCM
NC
XXXV
XXXVI

Fig. 5

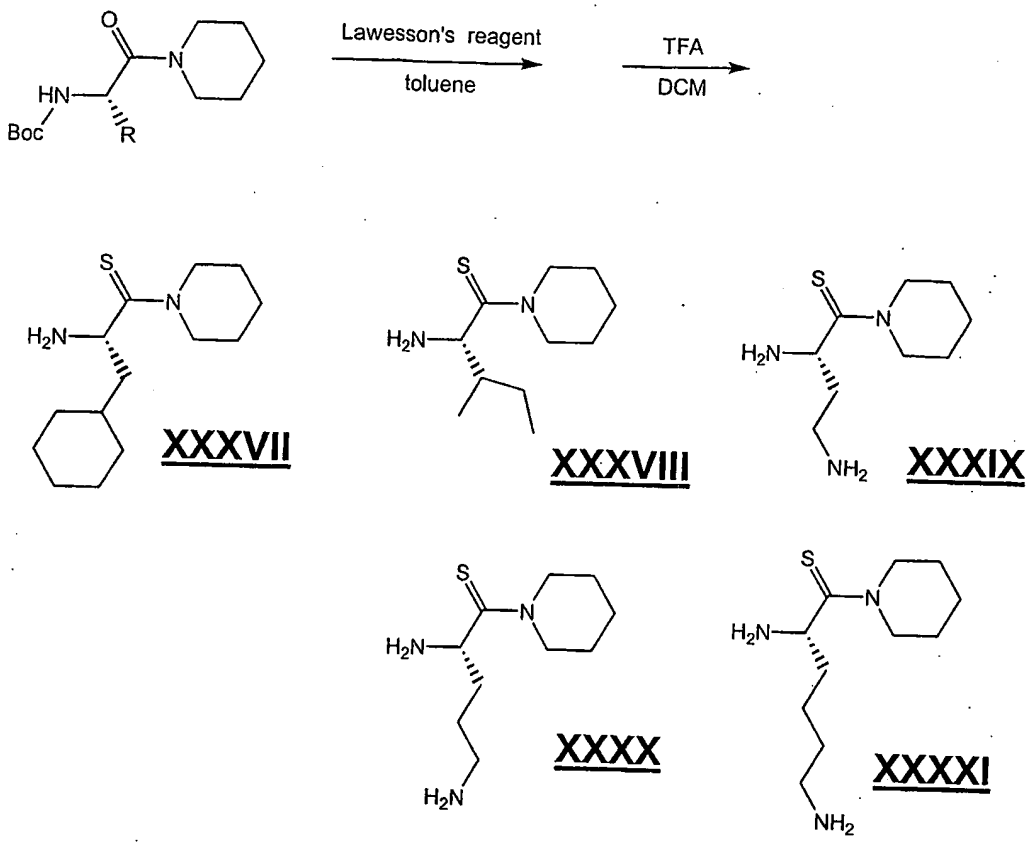
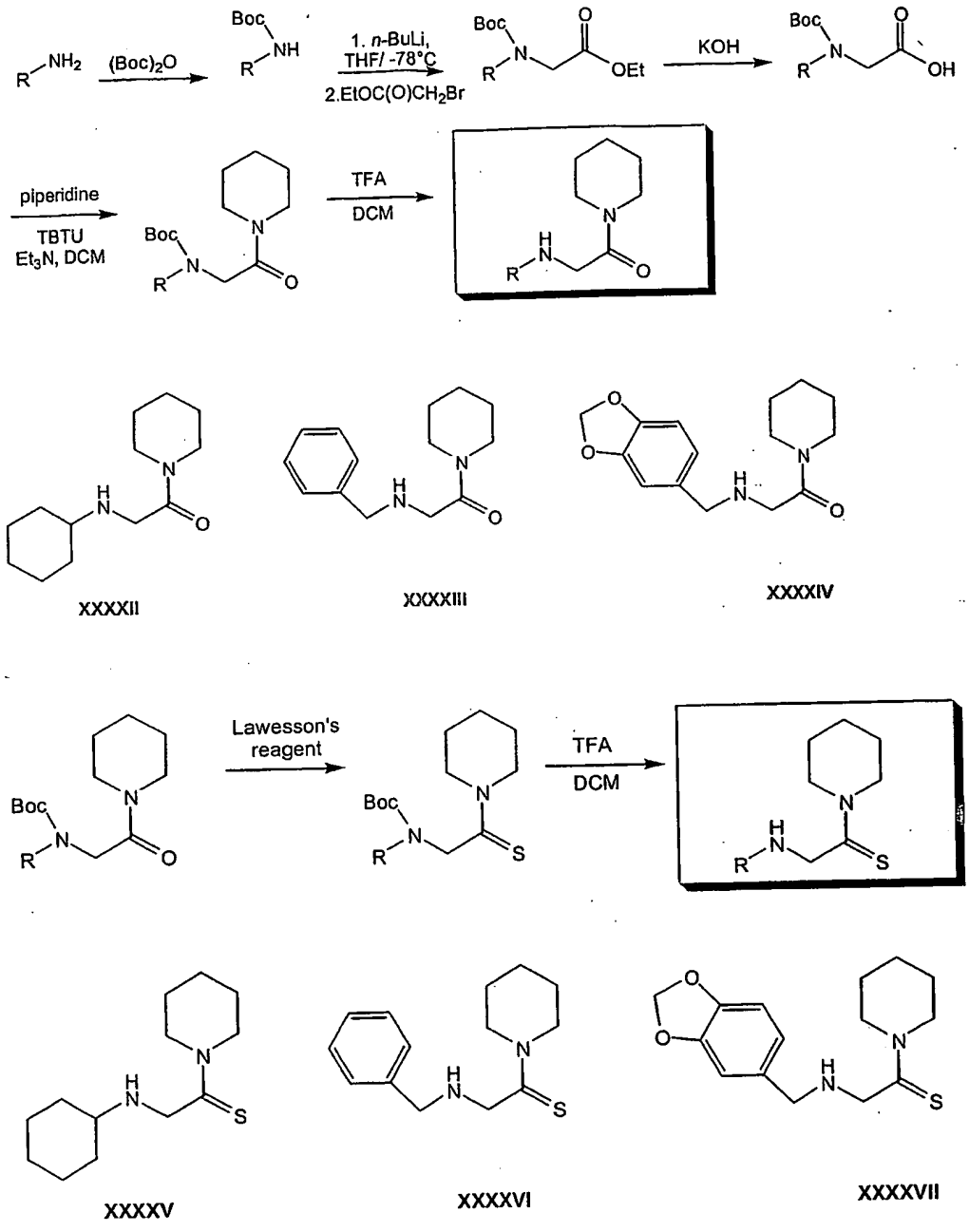

Lawesson's reagent
toluene
TFA
DCM
Boc
R
XXXVII
XXXVIII
XXXIX
XXXX
XXXXI

Fig. 6



XXXXII XXXXIII XXXXIV

XXXXV XXXXVI XXXXVII

Fig. 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/00792

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/18 C07D233/54 C07D317/58 A61K31/4453

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K SENTEN ET AL: "DEVELOPMENT OF POTENT AN DSELECTIVE DIPEPTIDYL PEPTIDASE II INHIBITORS" BIOORGANIC & MEDICIAL CHEMISTRY LETTERS, vol. 12, 2002, pages 2825-2828, XP002258184 see whole document, especially examples 18-25 ---	1-5,7, 24-30, 50-63
E	WO 03 035057 A (EVANS DAVID MICHAEL ;ASHWORTH DOREEN MARY (GB); FERRING BV (NL)) 1 May 2003 (2003-05-01) see general formula, formula 12,13,inter alia examples 11,20,21,26,27,38-40,49-52,97-100 and Tables --- -/--	1

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2003	03/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/00792

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	R BUIJSMAN ET AL: "Design and synthesis of a novel synthetic NAPAP-penta saccharide conjugate" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 9, 1999, pages 2013-2018, XP002258185 see compound 5 ---	1-5
X	KJL AUGUSTYNS ET AL: "Pyrrolidides:synthesis and structure-activty relationship as inhibitors of DPPPIV" EUROPEAN J MEDICINAL CHEMISTRY, vol. 32, 1997, pages 301-309, XP002258186 see compound 6b ---	1-5
X	JBM REWINKEL ET AL: "1-aminoisoquinoline as benzamidine isoster in the design of orally active thrombin inhibitors" BIORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, 1999, pages 685-690, XP002258187 see compound 16 ---	1-5
X	US 2 654 754 A (BRUCE WILLIAM F ET AL) 6 October 1953 (1953-10-06) see example 4 -----	45

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,50-63 (part)

Present claims 1-5,50-63 (part) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/apparatus/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 6-49.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/00792

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5,50-63 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 03/00792

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03035057 A	01-05-2003	WO 03035057 A1	01-05-2003
US 2654754 A	06-10-1953	NONE	